STUDIES RELATED TO THE CHEMISTRY OF NITRO COMPOUNDS AND RITTER REACTION
&
DEVELOPMENT OF SOME SYNTHETIC METHODS FOR ORGANIC SYNTHESIS

A Thesis Submitted
In Partial Fulfilment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

by

GNANASAMBANDAM KUMARAVEL

to the

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY, KANPUR

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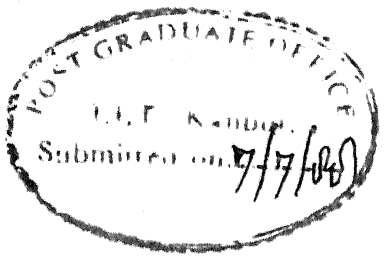

CERTIFICATE

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REACTION AND DEVELOPMENT OF SOME SYNTHETIC METHODS FOR ORGAN
SYNTHESIS'', by Mr. G. Kumaravel, has been carried out under
supervision and not submitted elsewhere for a degree.

Dr. Y.D. Vankar
Department of Chemistry
I.I.T., Kanpur-208016

July 1988

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY KANPUR, INDIA

CERTIFICATE OF COURSE WORK

This is to certify that Mr. G. Kumaravel has satisfactoril completed all the courses required for the Ph.D. degree programme These courses include:

Chm 502	Advanced Organic Chemistry II
Chm 505	Principles of Organic Chemistry
Chm 511	Physical Organic Chemistry
Chm 524	Modern Physical Methods in Chemistry
Chm 525	Principles of Physical Chemistry
Chm 545	Principles of Inorganic Chemistry
Chm 800	General Seminar
Chm 801	Special Seminar
Chm 900	Post-Graduate Research

Mr. G. Kumaravel has successfully completed his Ph.D. Qualifying Examination in August 1984.

N. Sathyamurthy
(Prof. N. Sathyamurthy)
Head,
Department of Chemistry
I.I.T. Kanpur-208016

S Sarkar
(Prof. S. Sarkar)
Convener
Departmental Post-Graduate Committee,
Dept. of Chemistry,
IIT-Kanpur-208 016

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Kanpur, India, under the supervision of Professor Y.D. Vankar.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

G. Kumaravel

G. KUMARAVEL

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G. KUMARAVEL

PREFACE

The thesis entitled: ''Studies related to the chemistry of nitro compounds and Ritter reaction and Development of some synthetic methods for organic synthesis'', consists of three chapters.

Chapter I deals with out studies on the synthesis and reactions of nitroolefins. To begin with, a brief introduction pertaining to the synthesis and reactions of nitroolefins is presented. Then, the synthesis of nitroolefins from alkenes using trifluoroacetic anhydride, ammonium nitrate and ammonium bromide has been described. Treatment of cyclopentene, cyclohexene, and cycloheptene with trifluoroacetic anhydride, ammonium nitrate and ammonium bromide followed by triethylamine was found to give the corresponding nitroolefins 61, 12 and 14 in moderate yields (50–65%). The synthesis of 2-nitrocyclohex-2-enone acetal (69) from 2-nitrocyclohexanone acetal (67) has been described. Successive treatment of 67 with n-BuLi, PhSeBr, and H_2O_2 gave 69 in 51% yield. Michael additions of various nucleophiles viz. thiophenol, ethyl phenylthioacetate and propargyl alcohol on 2-nitrocyclohex-2-enone acetal (69) and 3-nitrocyclohex-2-enone acetal (37) have been presented. Reaction of 2-nitroepoxy acetal (75) prepared from 2-nitrocyclohex-2-enone acetal (69) with sodium thiophenolate gave 2-keto-3-phenylthiocyclohexanone acetal (76) in 47% yield. Similar sequence of reaction on 37 gave 81 which undergoes dehydration to give 3-nitro-2-phenylthiocyclohex-2-enone (82). Utility of 2-nitro-3-propargyloxycyclohexanone

acetal (74), a Michael addition product from 67, in the synthesis of α-methylene butyrolactone 91 adapting radical chemistry has been presented.

In Chapter II, a brief introduction of the Ritter reaction and a literature survey of the ring opening of the cyclopropyl carbinols and cyclopropyl ketones with concomitant attack of nucleophiles have been presented. Our studies involving the cyclopropyl ketones viz. trans-1-benzoyl-2-phenylcyclopropane (49a), trans-1-acetyl-2-phenylcyclopropane (49b), trans-1-benzoyl-2-methylcyclopropane (49c) and bicyclo(4.1.0)heptan-2-one (50) and cyclopropyl carbinols viz. trans-1(1-hydroxybenzyl)-2-phenylcyclopropane (56a), trans-1(1-hydroxyethyl) 2-phenylcyclopropane (56b), trans-1(1-hydroxybenzyl)-2-methylcyclopropane (56c), trans-1(1-hydroxy-1-methylbenzyl)-2-phenylcyclopropane (57) and bicyclic alcohols viz. bicyclo(3.1.0)hexan-2-ol (58a), bicyclo(4.1.0)heptan-2-ol (58b), bicyclo(5.1.0)octan-2-ol (58c), 5-methyl bicyclo(3.1.0)hexan-2-ol (58d) and 6-methyl bicyclo(4.1.0)-heptan-2-ol (58e) with two nitriles viz. acetonitrile and acrylonitrile in the presence of concentrated sulphuric acid have been described in detail. In the case of ketones 49a,b the cyclopropyl ring was opened by both aceto and acrylonitrile and the corresponding Ritter reaction products i.e. amides 51a,b and 52a,b were obtained in moderate yields (45-64%). On the other hand ketones 49c and 50 were found to be resistant to the nitrile attack under the present experimental conditions. Treatment of alcohols 56a-c under similar

conditions gave the corresponding N-acyl homoallylamines 59a-c, 60a-c with E-stereochemistry. Tertiary alcohol 57 was also found to undergo ring opening to give N-acyl homoallyl amines 63 and 64 with acetonitrile and acrylonitrile respectively. On the other hand bicyclic alcohols 58a-c were found to give a mixture of two products viz. the products having cyclopropane ring intact 65a-c and 67a-c and the ring expanded products 66a-c and 68a-c. However 58d,e gave exclusively ring expanded products 66d,e. A plausible mechanism to explain the formation of different products has been proposed.

Chapter III has been divided in to two parts. In Part A development of synthetic methods based on sodium iodide-N-chloro-succinimide and sodium iodide-chlorotrimethylsilane have been presented. Synthesis of N-iodosuccinimide from NCS and sodium iodide and its utility in the synthesis of α-iodocarbonyl compounds have been described in Part A(i). To begin with, a brief literature survey for the preparation and uses of NIS has been presented. Treatment of NCS and NaI in acetone gave almost quantitative yield of NIS. Advantages of this method over the existing method of its preparation have been described. To test the applicability of this reagent system, a known reaction i.e. preparation of trans-1,2-iodoacetates from olefins using NIS and acetic acid was carried out with both NCS-NaI and commercial NIS for comparison. Treatment of alkenes 30a-d and 32 with both NCS-NaI and commercial NIS gave the corresponding iodoacetates 31a-d, 33 and 34 in comparable yields. A new method of preparation of α-iodoketones from enol silyl ethers

using NCS-NaI has been described. Treatment of enol silyl ethers 35a-c, 37 and 39 gave α-iodoketones 36a-c, 38 and 40 in (71-85%) yields. Once again for comparison, results of these reactions using commercially available NIS have been presented. The yields were found to be comparable.

In Part A(ii), synthesis of 1,4 and 1,5-diketones from ene-diones and cyclopropyl diketones using NaI-chlorotrimethylsilane has been presented. Treatment of ene-diones 67-72 and cyclopropyl diketones 79a,b with NaI-chlorotrimethylsilane gave 1,4 and 1,5-diketones 73-78 and 84a,b respectively under practically neutral and mild conditions in high yields (89-98%). A rationale for the success of this reaction has been presented.

In Part B, Pd(0) catalyzed allylic alkylation of substituted allyl acetates has been presented. To begin with a brief introduction to the Pd(0) catalyzed C-C bond formation using allyl acetates has been described. In the present study, phenylthio substituted allyl acetates viz. 1-acetoxy-2-phenylthiocyclopent-2-ene (30a) and 1-acetoxy-2-phenylthiocyclohex-2-ene (30b) under Pd(0) catalyzed conditions with diethyl sodiomalonate were found to give the corresponding alkylated products 31a,b in moderate yields (66% and 73%) under mild reaction conditions. Similarly allyl acetates with cyano substitution viz. 2(1-acetoxyheptyl)acrylonitrile (37a) and 2(1-acetoxybenzyl)acrylonitrile (37b) with diethyl sodiomalonate under Pd(0) catalyzed conditions gave the corresponding alkylated

products 38a,b in high yields (93 % and 91%). These reactions were found to proceed in a highly regio and stereoselective manner. Nucleophilic reaction on 4-acetoxy-2-phenylthiocyclopent-2-enone (46) in the presence of Pd(0) gave a mixture of products, however in the absence of Pd(0) it was found to give the rearranged product 47 in 54 % yield. A possible extention of this reaction for the synthesis of prostaglandin D_2 metabolite 52 has been described.

CONTENTS

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CHAPTER - I

SYNTHESIS AND REACTIONS OF NITROOLEFINS

I.1 Introduction

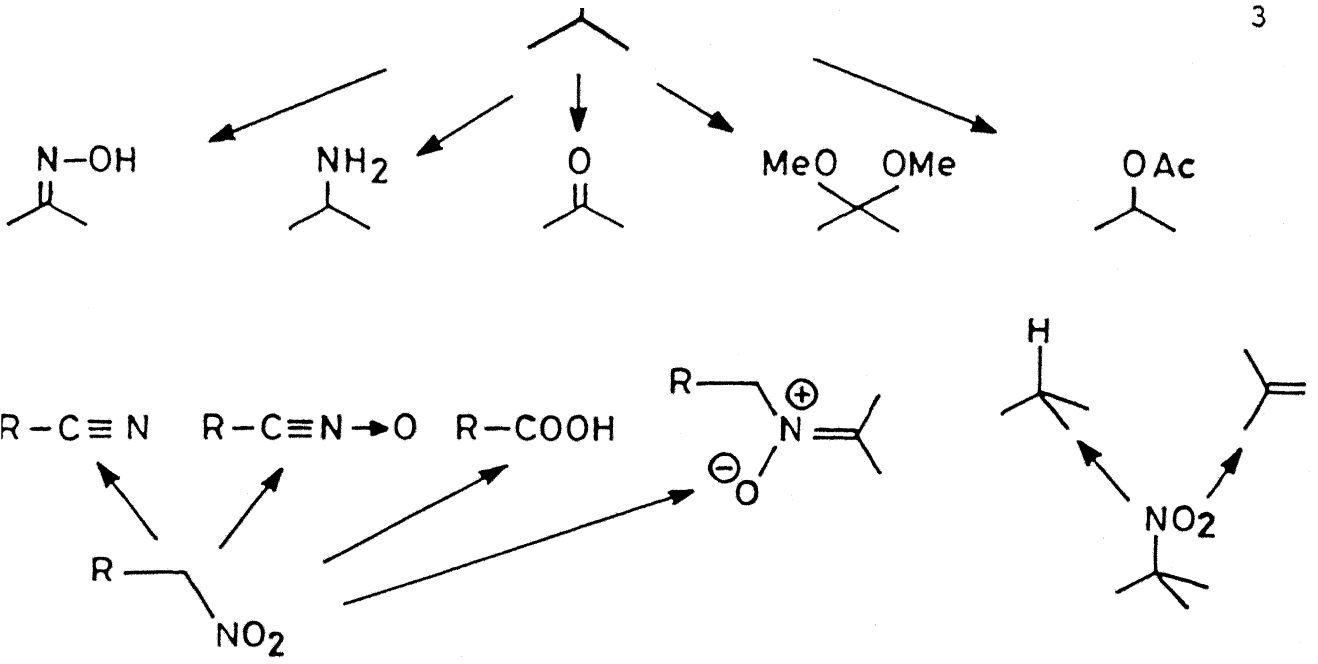
The nitro group is a powerful electron withdrawing substituent, and this property dominates the chemistry of all molecules containing this functional group. The many routes from nitro aliphatic compounds to non-nitro containing products (Scheme I.1), together with their reactivity-donor activity of nitronates, acceptor activity of nitroolefins-provides an array of possibilities which is unique among functional groups in organic chemistry.

The chemistry of aliphatic nitro compounds has recently received much attention because of their importance in organic synthesis. In particular, the focus is on conjugated nitroolefins as they have been demonstrated to be valuable intermediates in the synthesis of a variety of structures.[1] Apart from being powerful dienophiles in the Diels-Alder reactions, these electrophilic alkenes readily undergo reactions with many different nucleophiles.

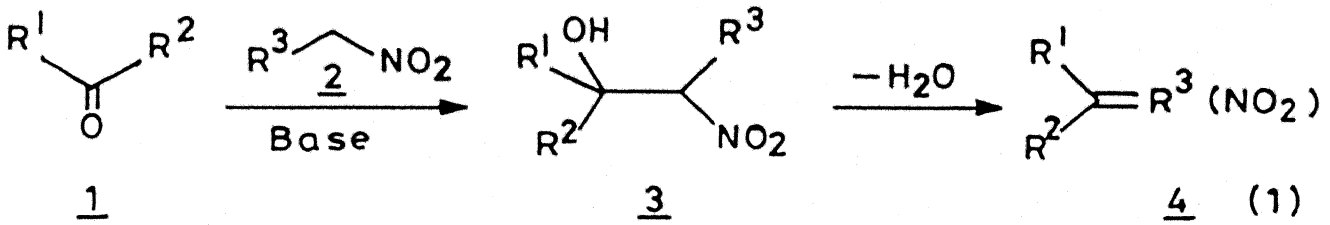
The uniqueness of such a synthon has been responsible for the numerous procedures which have recently appeared in the literature for its synthesis. The commonly used starting substrates are aldehydes, ketones, alkenes, nitroalkanes etc. Some of the methods of preparation are shown in Scheme I.2.

The most versatile preparation of nitroolefins 4 involves the Henry condensation reaction of an aldehyde or ketone 1 with a nitroalkane 2 followed by dehydration of the resulting β-nitro alcohol 3[1a] (eq. 1, Scheme I.2). The Henry condensation is effected under mild basic condition. Recently several reagents including dicyclohexylcarbodiimide (DCC),[2] pivaloyl chloride,[3] methanesulfonyl chloride,[4] phthalic anhydride[5] have been used for the dehydration step. Barton[6] reported the direct conversion of ketone 5 to nitroolefin 6 using nitromethane and ethylenediamine as a catalyst (eq. 2, Scheme I.2).

The drawback of the Henry condensation reaction is that the formation of β-nitro alcohols 3 by the condensation of aldehydes and ketones with nitroalkanes is limited primarily to the synthesis of acyclic nitroolefins. Intramolecular condensation to give cyclic β-nitro alcohols is difficult due to the inaccessibility of the acyclic nitro carbonyl compounds. However, there are a few reports[7] of intramolecular Henry condensation type as shown in eq. 3, Scheme I.2 to get compounds of type 9.



Scheme I.1



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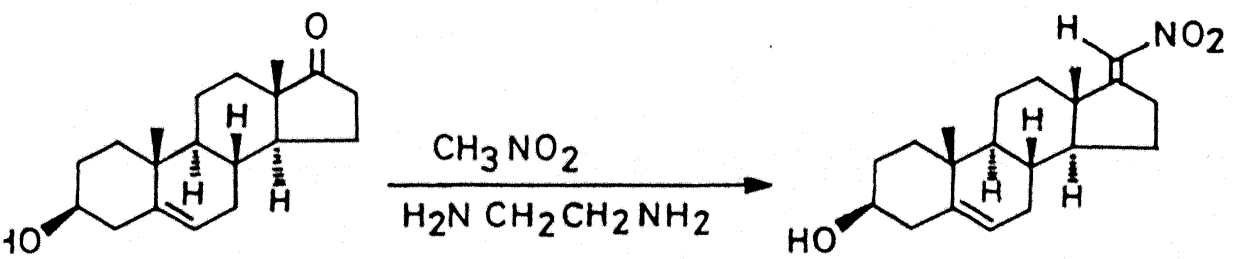
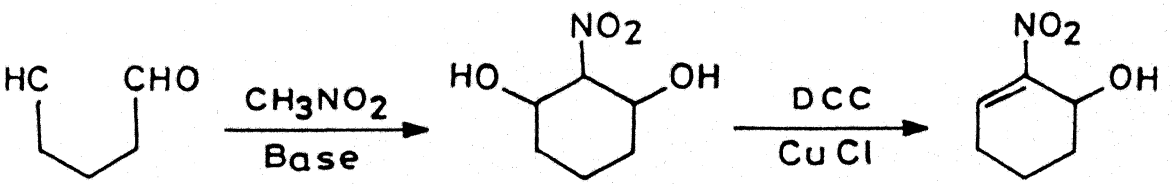


5 6 (2)

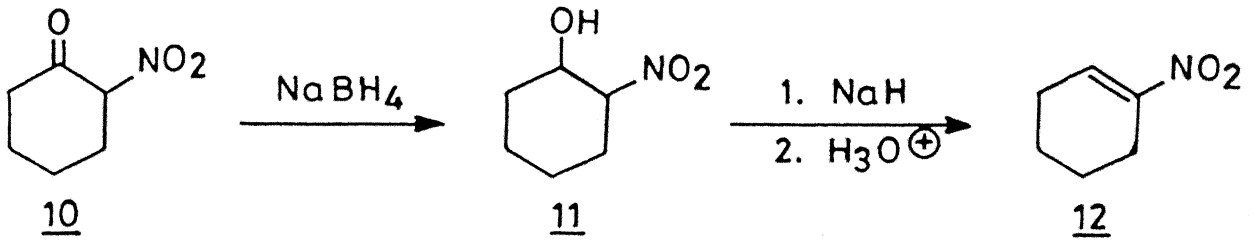


7 8 9 (3)

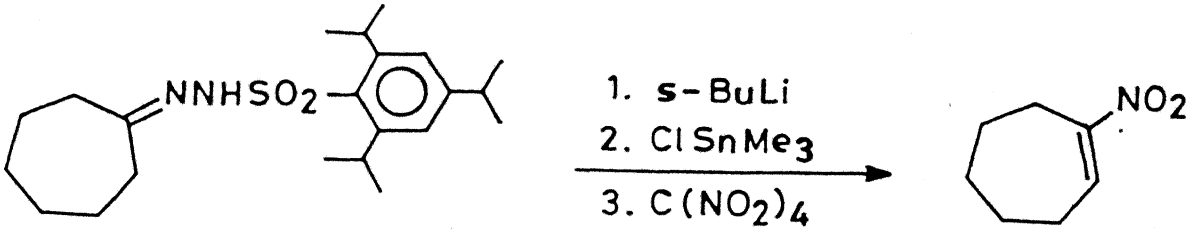
Scheme I.2 (contd.)

Synthesis of cyclic nitroolefins has received considerable attention. As a result, a number of precursors have been used for this purpose.Zajac and coworkers[8] have reported a synthesis of cyclic nitroolefin 12 starting from cyclic α-nitroketone 10 (eq.4, Scheme I.2). On the other hand Corey[9] converted cycloheptanone to 1-nitrocycloheptene using vinyl anion derived from 13 (eq. 5, Scheme I.2).

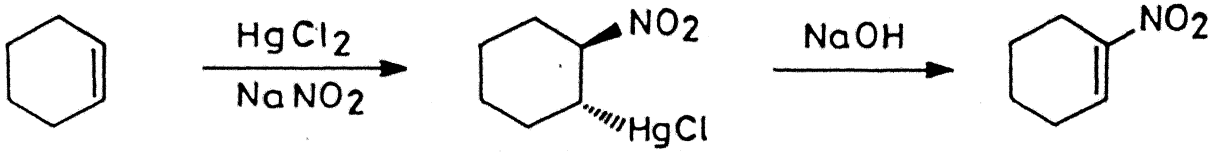
Alkenes are potent starting materials for the synthesis of cyclic nitroolefins. The earliest method was the reaction of olefins with dinitrogen tetroxide followed by treatment with base.[10] Corey[11] converted alkenes to nitroolefins using mercuric chloride and sodium nitrite in aqueous solution. The intermediate nitromercurial 15 was subjected to a novel base catalysed elimination to give nitroolefin 12 starting from cyclohexene (eq. 6, Scheme I.2). Tomoda[12] and Seebach[13] have utilized selenium chemistry in the preparation of nitroolefins. For example, cyclohexene reacted with phenylselenyl bromide, silver nitrite and mercuric chloride to give 16. On oxidation with hydrogen peroxide 16 was converted into 12 (eq. 7, Scheme I.2). Sakakibara[14] and coworkers have reported that peroxytrifluoroacetic acid oxidation of α-chloro or α-bromo oximes which are readily available from alkenes via the addition of nitrosyl chloride (bromide) in the presence of hydrochloric (bromic) acid, produced the corresponding nitroolefins. Thus, for example, oxidation of 17 gave 12 (eq. 8, Scheme 1.2). Nitroalkanes have been converted into nitroolefins using selenium



10 11 12 (4)



13 14 (5)



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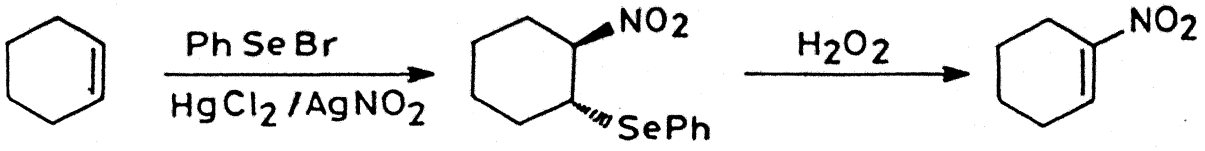
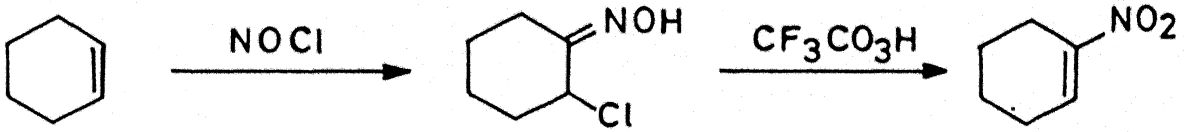


16 (7)



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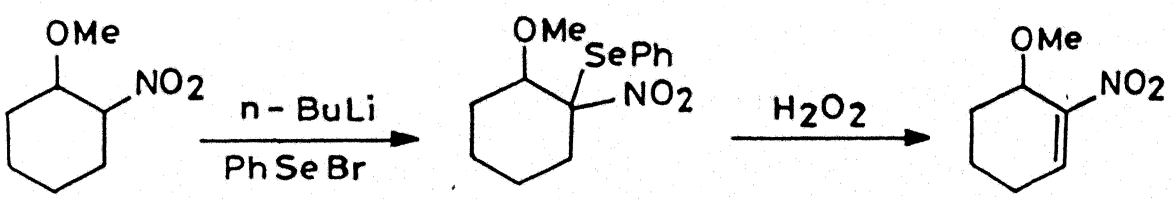


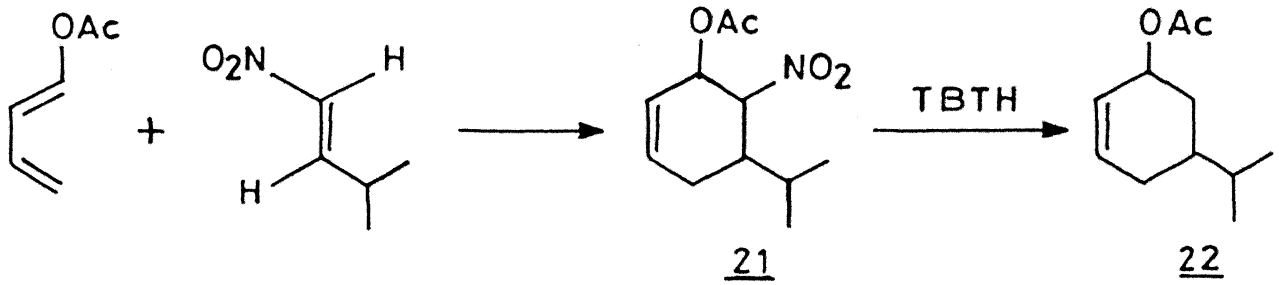
18 19 20 (9)

Scheme I.2

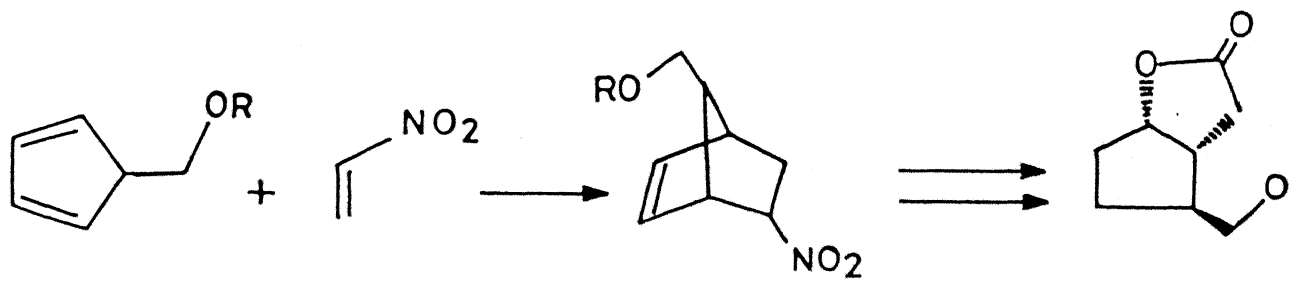
chemistry.[15] For example, oxidative elimination of nitroselenide 19 prepared from 18 gave 20 (eq. 9, Scheme I.2).

Nitroolefins are potent dienophiles and they generally require low temperature for the Diels-Alder reaction to occur. Furthermore, the nitro group is very effective in controlling the regiochemistry of the reaction with unsymmetrical dienes. Ono[16] has used such chemistry to prepare 22. The initially formed Diels-Alder adduct 21 was chemoselectively denitrated with tri-n-butyltin hydride (TBTH) to produce 22 (Scheme I.3). Ranganathan and co-workers[17] have shown that nitroethylene is a convenient reagent for (4 + 2) cycloadditions. The cycloadduct 25, formed from 23 and nitroethylene (24), has been further elaborated to produce prostanoids (Scheme I.3). Similarly cycloadducts 26 obtained from furan and β-nitroacrylate have been utilised for the synthesis of Showdomycin 27[18] (Scheme I.3). Interestingly, nitroolefins behave as 4π component in a (4 + 2) cycloaddition with olefins in the presence of Lewis acids. For example, nitrocyclohexene was reacted with cyclohexene to give 28[19] (Scheme I.4).

In the area of nitroolefin chemistry Corey et al.[20] have recently described the synthesis and reactions of two nitro enones viz. 3-nitro-2-cyclohexenone (31b) and 3-nitro-2-cyclopentenone (31a) for the first time. Peroxytrifluoroacetic acid oxidation of oximes 29a and 29b gave 30a and 30b and these nitroalcohols were directly oxidized *in situ* with pyridinium chlorochromate (PCC). The nitro enones 31 were found to be powerful dienophiles in the Diels-Alder

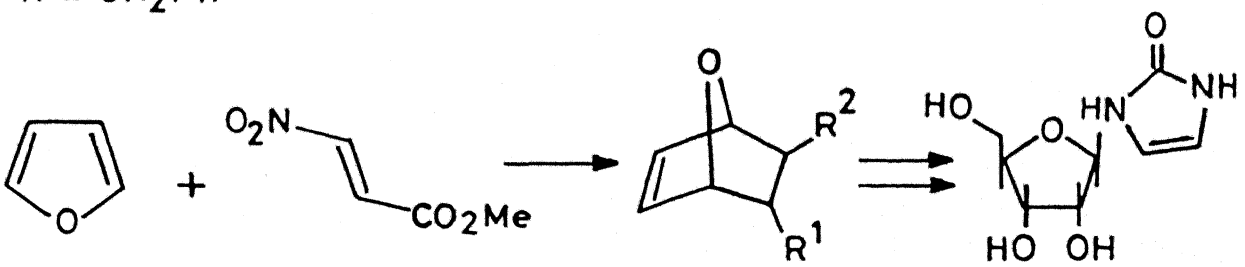


21 22



23 24 25

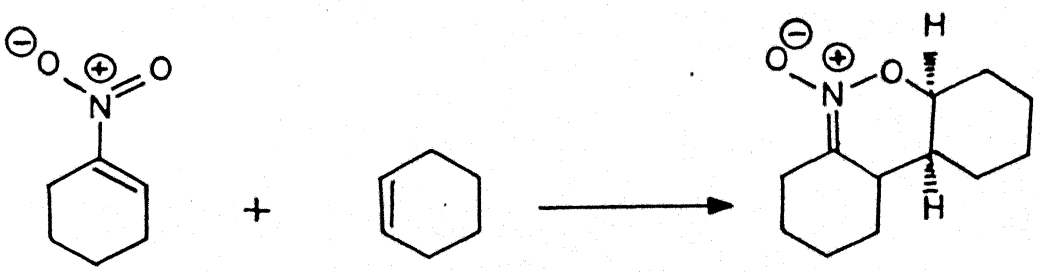
R = CH_2Ph



26a $R^1 = NO_2$, $R^2 = CO_2Me$ 27

b $R^1 = CO_2Me$, $R^2 = NO_2$

Scheme I.3



28

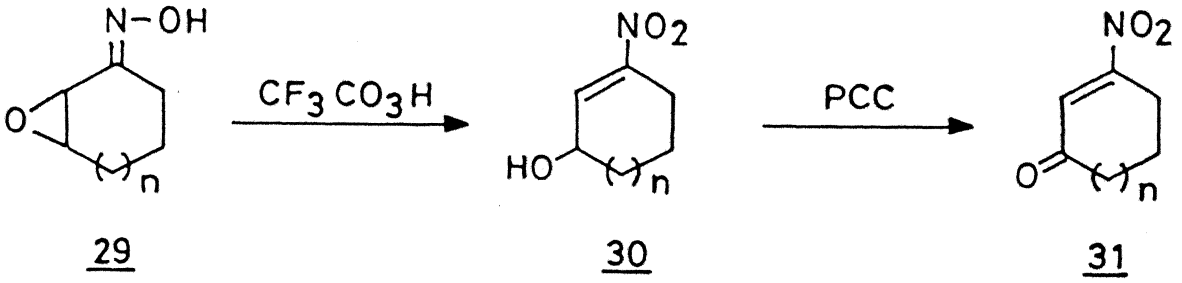
Scheme I.4

reaction. The powerful electron withdrawing nitro group overwhelms the directing effect of the keto group in the reaction with dienes. Thus for example, 31b was reacted with 32 to produce 33. This was not isolated but converted directly to 34 by reaction with 1,5-diazabicyclo(3.4.0)nonene-5 (DBN) (Scheme I.5). This important nitro enone 31b has been synthesised in our group by Bawa[21] in a simple manner adapting Corey's nitromercuration chemistry. 36 was reacted sequentially with mercuric chloride-sodium nitrite, sodium hydroxide to produce 37 which on hydrolysis using 5% aqueous sulphuric acid gave 31b (Scheme I.6).

Also, nitroolefins have been well documented as versatile and prominent, Michael acceptors in conjugated addition reactions. Variety of nucleophiles have been added to nitroolefins. Yoshikoshi[1e] demonstrated that the condensation of enol silanes with nitroolefins is a general approach to 1,4-dicarbonyl compounds. For example, the condensation of 38 and 39 in the presence of a Lewis acid produced 40 (Scheme I.7).

Seebach and coworkers[22] have introduced 2-nitro-3(pivaloyloxy)propene (41) as a highly versatile reagent for multicomponent coupling reactions. For example, the reaction of 41 with enolate derived from ethyl acetate 42 gave 43. Subsequent reaction of 43 with enol silyl ether 44 gave 45 (Scheme I.7).

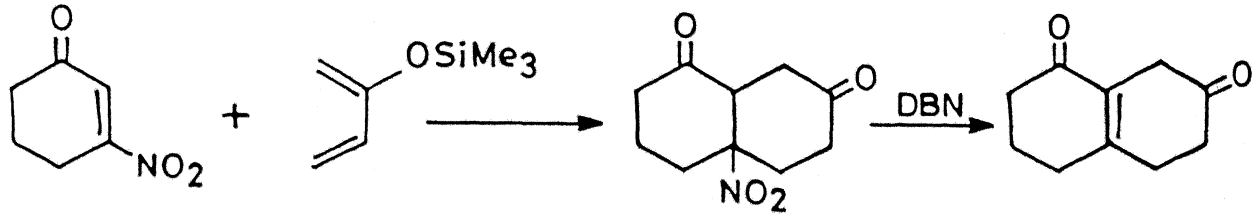
Recently prostaglandin 50 has been synthesised by the Michael addition of enolate ion, generated *in situ* from 46 by the



29 30 31

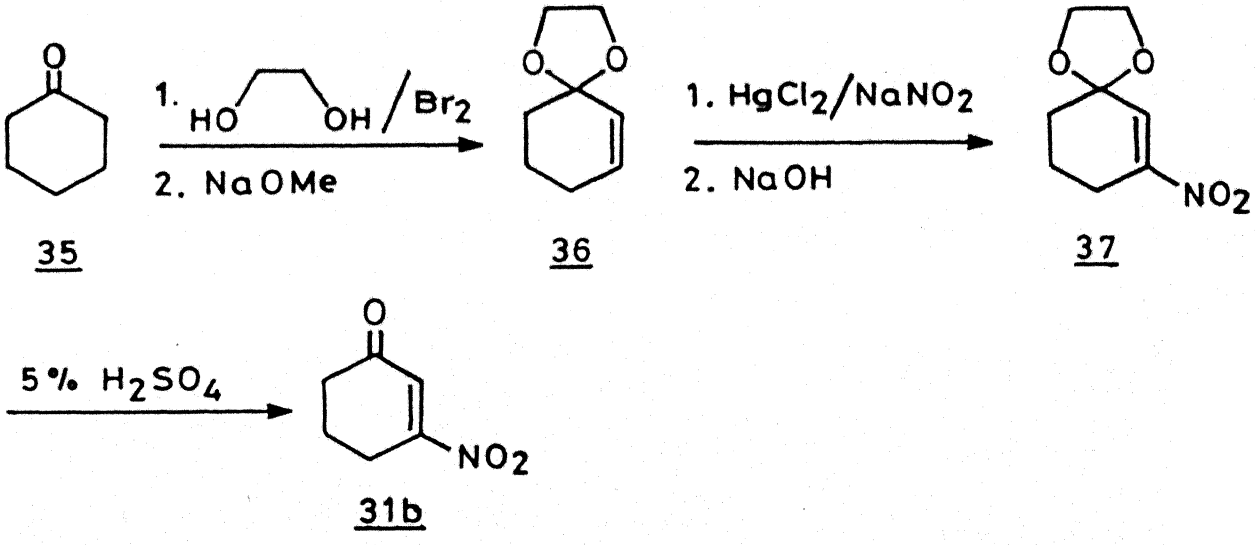
a n = 0

b n = 1



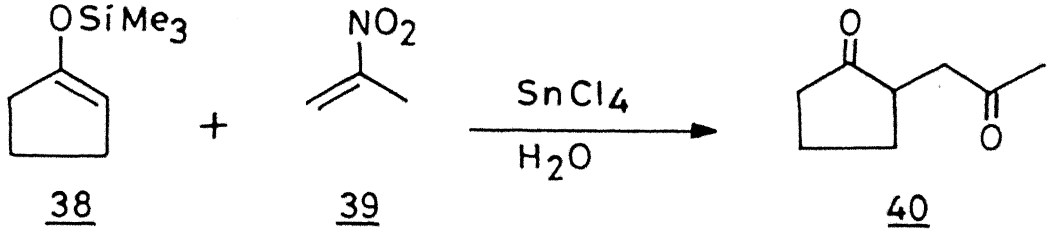
31b 32 33 34

Scheme I.5

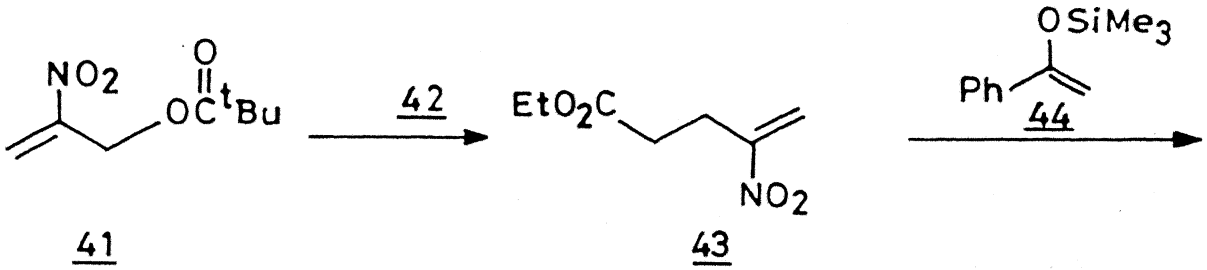


35 36 37 31b

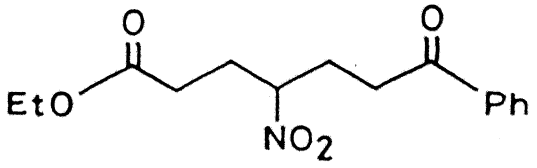
Scheme I.6



38 39 40



41 43



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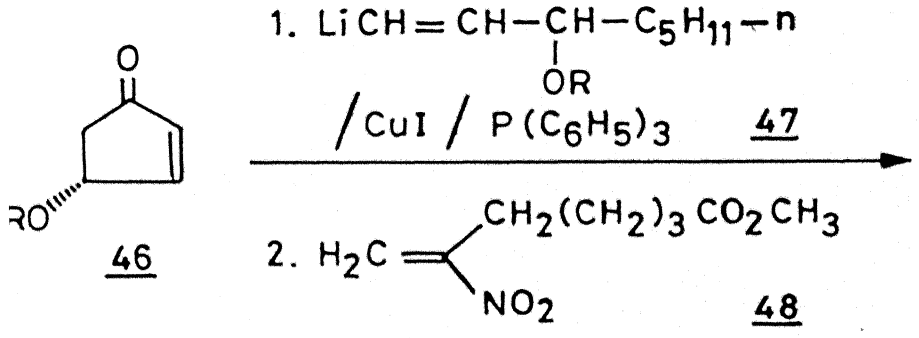
Scheme I.7



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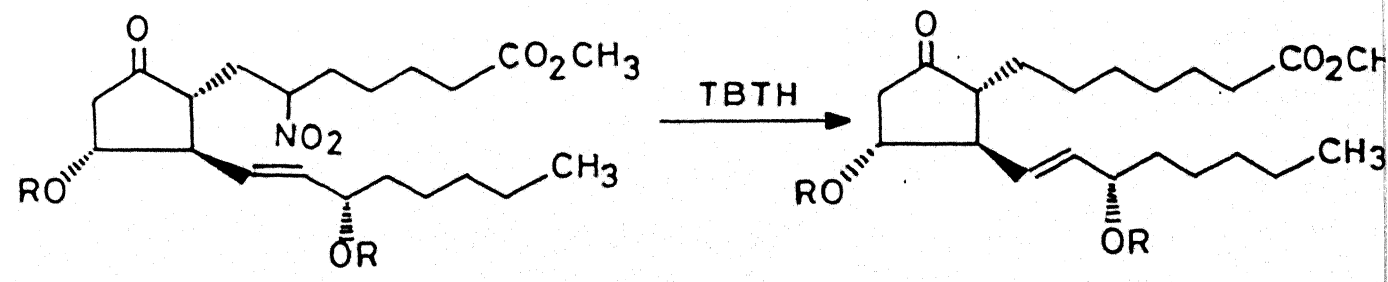


49 50

Scheme I.8

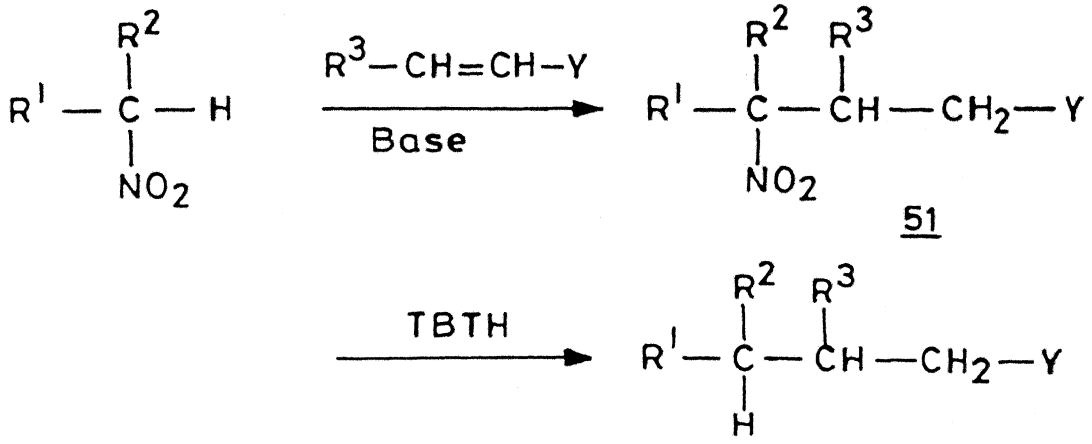
addition of cuprate 47 to the nitroolefin 48. Subsequent removal of the nitro group from 49 using TBTH gave 50[23] (Scheme I.8).

Not only carbon nucleophiles but nitrogen,[24,25] sulphur,[3b] oxygen[26,31] and phosphorus[27] centered nucleophiles have also been successfully added to nitroolefins. Besides these, Barton[28] has demonstrated the addition of carbon centered radicals to nitro-olefins.

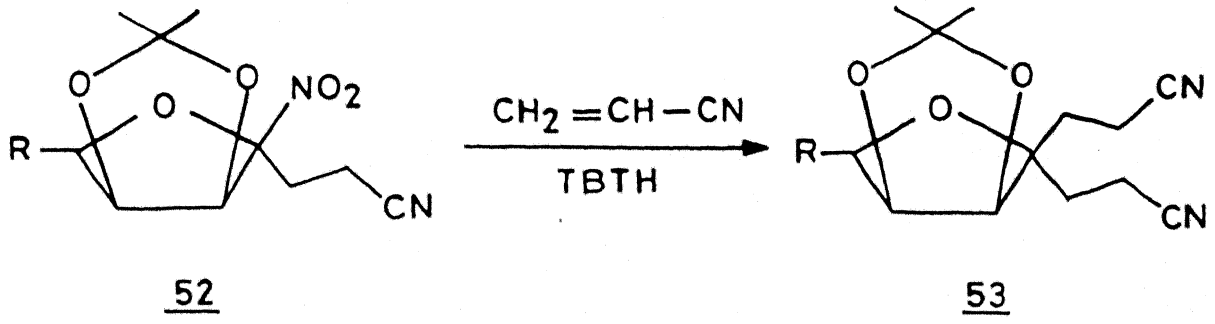
The saturated secondary nitroalkanes have been shown to undergo Michael reaction with activated olefins under basic conditi ons. The subsequent removal of the nitro group from the adduct 57 using tri-n-butyltin hydride (TBTH) provides a useful method for the preparation of alkylated products[29] (Scheme I.9).

As reductive cleavage of aliphatic nitro compounds with TBTH proceeds via alkyl radical intermediates, nitrocompounds are used as precursors to generate alkyl radicals. Such radical intermedia-tes undergo both an inter and intramolecular radical addition to electron defficient olefins, to give a variety of compounds. Some examples of this chemistry are shown in Scheme I.10. The radical generated from nitro sugar 52 was reacted with acrylonitrile to give C-glycoside 53 with a quarternary carbon at C-1[30]. Compound 57 was prepared from nitroolefin 54 employing radical cyclization.[3]

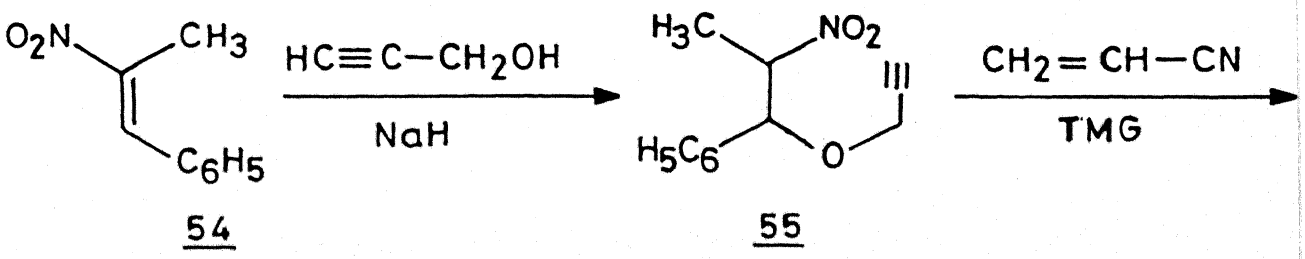
Consideration of olefins as easily available precursors for the synthesis of nitroolefins, the present study was under taken for a simple alternative procedure for their synthesis. For this



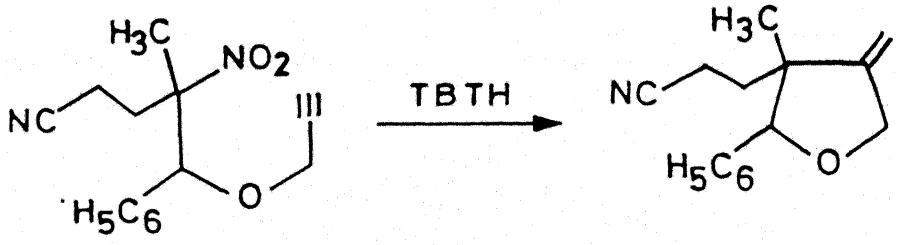
Scheme I.9



52 53



54 55



56 57

Scheme I.10

purpose a combination of ammonium nitrate and trifluoroacetic anhydride (TFAA) was used as a good source of nitronium ion. This reagent system has been earlier used to oxidise aliphatic hydrocarbons,[32] nitrate aromatic systems,[33] oxidize phenolic compounds,[33] convert enol acetates to nitroketones[34] and dienes to vinyl nitro compounds.[35]

Reaction of ammonium nitrate with anhydrides appears to bear close resemblance to the well known nitrating agent 'acetyl nitrate'. Acetyl nitrate may be generated <u>in situ</u> from acetic anhydride with nitric acid. With trifluoroacetic anhydride and ammonium nitrate,

$$(CH_3CO)_2O + HNO_3 \longrightarrow CH_3\overset{O}{\overset{\|}{C}}O-NO_2 + CH_3COOH$$

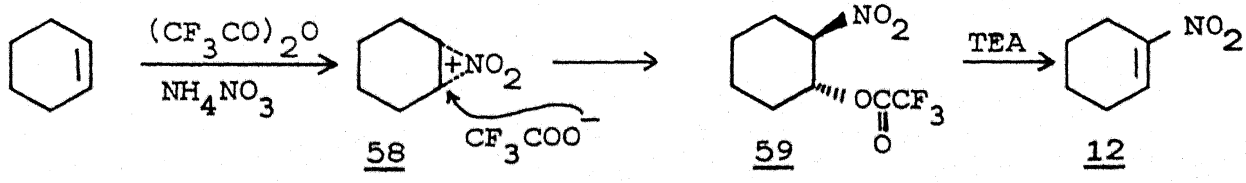
one would get trifluoroacetyl nitrate which is much more efficient and powerful nitrating agent than acetyl nitrate due to a good leaving group in the form of trifluoroacetate anion. Alkenes were used

$$(CF_3CO)_2O + NH_4NO_3 \longrightarrow CF_3\overset{O}{\overset{\|}{C}}O-NO_2 + CF_3COONH_4$$

to test the applicability of this reagent system for the synthesis of nitroolefins. The results of this investigation are presented in 'results and discussion' section of this chapter.

I.2 Results and Discussion

In the introduction part of this chapter it has been described that a mixture of trifluoroacetic anhydride (TFAA) and ammonium nitrate is a good system for the generation of nitronium ion. The present study dealtwith the utility of this reagent system for a simple synthesis of nitroolefins starting from alkenes, readily available starting materials. Sequential treatment of olefins with TFAA-ammonium nitrate and triethylamine was found to give nitroolefins. A plausible mechanism for the formation of 1-nitrocyclohexene (12) from cyclohexene using this reagent system is shown in Scheme I.11. The intermediate, nitrotrifluoroacetate 59 was treated with triethylamine to get 12.



58 59 12

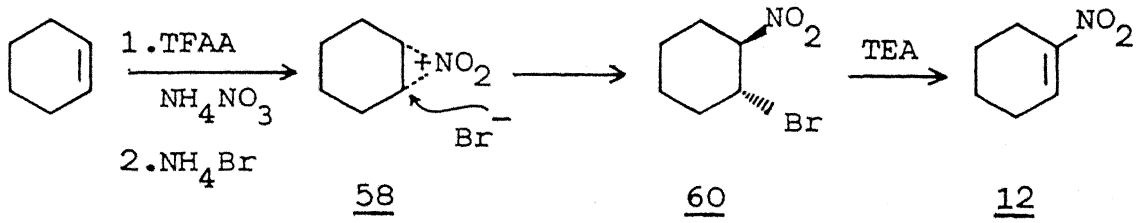
Scheme I.11

The reaction of cyclohexene with TFAA-ammonium nitrate in $CHCl_3$ at 0^oC for 8 h gave quantitative yield of nitrotrifluoroacetate 59. IR spectrum of 59 showed strong absorptions at 1780 cm^{-1} and 1550 cm^{-1} indicating the presence of trifluoroacetate and nitro groups. Treatment of the crude nitrotrifluoroacetate with triethylamine gave 1-nitrocyclohexene (12) in 40% yield. The spectral

properties of the product 12 were similar to the one reported in the literature.[12b]

In order to improve the yield of the above reaction, various bases like NaH, NaOMe, K_2CO_3, KO^tBu and CH_3COOK for elimination, were tried. However, none of these bases was found to affect the yield of the product. Interestingly, in the literature[36] also elimination of CF_3COO^- has not been found to give good yields of the product. Hence a possibility of replacing the trifluoroacetate group by some other leaving groups like bromide or iodide was considered and tried. To replace the trifluoroacetate group by iodide, the nitrotrifluoroacetate 59 was reacted with sodium iodide in refluxing acetonitrile. The starting nitrotrifluoroacetate was recovered back even after prolonged reflux. However, if the iodide or bromide ion is present in the reaction medium then it would react with nitronium ion intermediate 58, faster than the trifluoroacetate ion, by virtue of its being better nucleophile than trifluoroacetate ion, to give bromo(iodo) nitro compound.

The feasibility of this hypothesis was successfully realised when the reaction of cyclohexene with two equivalent of ammonium nitrate and two equivalent of TFAA in the presence of four equivalent of ammonium bromide followed by treatment with triethylamine was found to give 65 % of 1-nitrocyclohexene (12) (Scheme I.12).



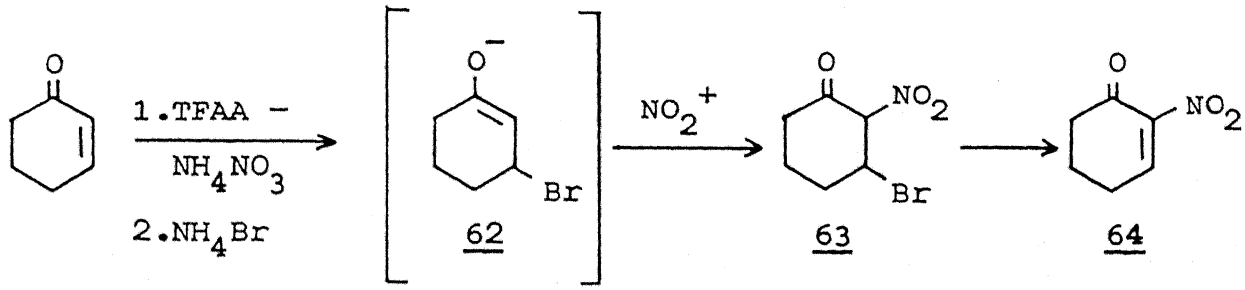
58 60 12

Scheme I.12

Similarly, the reaction of cyclopentene and cycloheptene with this reagent system gave 1-nitrocyclopentene(61) and 1-nitrocycloheptene(14) in 50%and 63 % yields respectively.

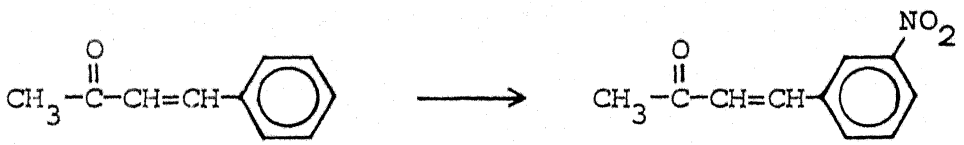
The usefulness of nitroolefins in organic synthesis has been described in the introduction part of this chapter. Nitroolefinic compounds possessing more functional groups in the vicinity of the vinyl nitro function could extend the use of nitroolefin chemistry. This fact has been amply demonstrated by Corey[20] by introducing 3-nitro-2-cyclohexenone(31b)for the first time. The powerful dienophilic character of this synthon was also demonstrated by Corey. The keto and the nitro functionalities, both being powerful electron withdrawing groups, brought out interesting features in 31b especially because they are present at different ends of the olefin. It was of special interest to us to prepare and find out the behaviour of 2-nitro-2-cyclohexenone (64) as it would be complementary to 31b. The use of TFAA-ammonium nitrate reagent system for this purpose was considered a possibility while dealing with cyclohexenone as the precursor. It was expected that the bromide ion may add on to cyclohexenone in a Michael fashion to

give enolate ion 62 which can be trapped *in situ* by the nitronium ion present in the system. The intermediate bromonitro compound 63 could be converted to 64 in the presence of a base (Scheme I.13 However, the reaction of cyclohexenone with TFAA-ammonium nitrate,



Scheme I.13

and ammonium bromide gave a mixture of products which could not be purified to obtain any compound in pure state. Another substrate subjected to similar reaction condition was 65 which gave exclusively the aromatic nitrated product 66 (cf. experimental section).

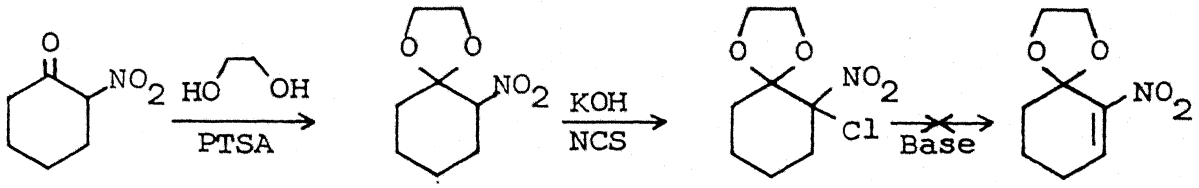


65 66

Considering the potential importance of 2-nitro-2-cyclohexenone (64), 2-nitrocyclohexanone (10) was considered as an alternative substrate for its preparation. Treatment of 2-nitrocyclohexanone with a base such as NaH or BuLi followed by N-chlorosuccinimide (NCS), N-bromosuccinimide (NBS) or diphenyl disulphide

did not a yield a clean reaction product in our hand. Deprotonation of the proton adjacent to nitro group followed by the attack of electrophiles is not well precedented in the literature,[37] perhaps because of the sensitiveness of α-nitroketones towards bases.

In order to overcome this difficulty the corresponding acetal 67 was prepared following the literature procedure[38] in 69 yield. Treatment of 67 with KOH in dioxan-water mixture followed by NCS gave 2-chloro-2-nitrocyclohexanone acetal(68).[39] Several bases such as Et_3N, NaH and KO^tBu were allowed to react with 68

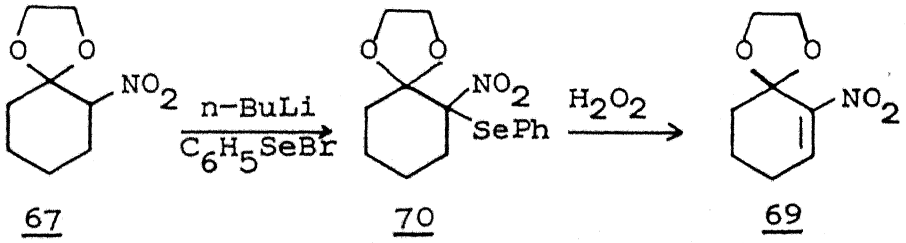


10 67 68 69

in order to bring about dehydrohalogenation to obtain 69. The first two bases did not have effect on 68 and all the starting material was recovered. However, with KO^tBu, surprisingly the nitro acetal 67 was obtained back.

Thermal elimination of sulphoxides[40a] and selenoxides[40b] to give olefins has been recently well developed and utilized in organic synthesis. Thus treatment of 67 with n-BuLi followed by PhSSPh gave a crude product which was *in situ* further treated with 30% H_2O_2.

The crude reaction product indicated it to be a complex mixture, purification of which proved to be very difficult. Finally 69 was obtained by using selenium chemistry. Thus, when 67 was deprotonated with n-BuLi at 0°C followed by treatment with PhSeBr at 0°C for 1 h and subsequently with 30% H_2O_2 for 5 h gave a crude product. Purification of this mixture by column chromatography on silica gel gave 69 in 51% yield (Scheme I.14). The structure of 69

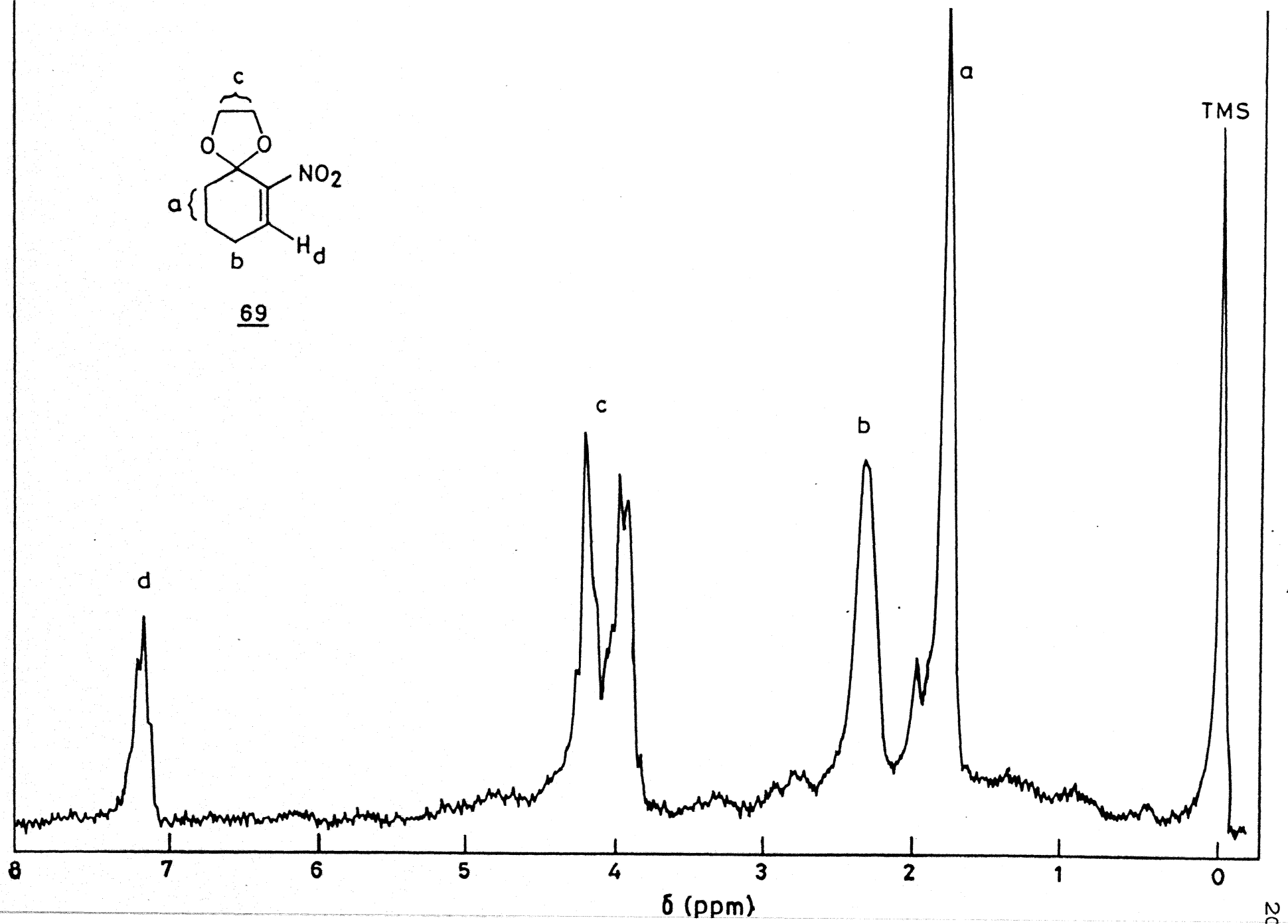


67 70 69

Scheme I.14

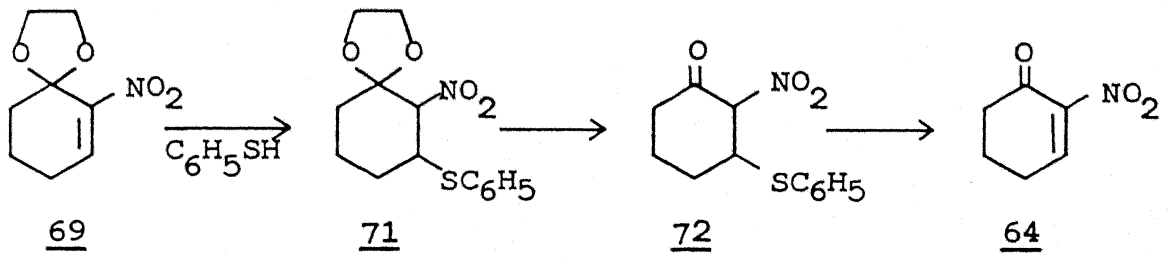
was confirmed on the basis of its spectral and analytical data. Thus, in IR spectrum a strong absorption at 1510 cm^{-1} was observed indicating the presence of vinyl nitro group. Its ^1H NMR spectrum (Fig. I.1) showed absorptions at δ 1.8 (m, 4H), 2.2-2.55 (m, 2H, allylic CH_2), 3.85-4.35 (m, 4H, acetal CH_2), 7.2 (m, 1H, vinylic). Further, its mass spectrum showed a molecular ion peak at 185. To our knowledge this compound is not known in the literature.

Having obtained 69, attention was focussed towards its hydrolysis to get 2-nitro-2-cyclohexenone (64). Reaction of 69 with 5% aqueous sulphuric acid (usual hydrolysis condition) gave a mixture


c
O
O
NO2
a
b
Hd
69
a
TMS
c
b
d
8
7
6
5
4
3
2
1
0
δ (ppm)

of products. A recently developed method[41] for acetal hydrolysis using NaI-BF_3.Et_2O reagent also gave a mixture of products. This may be due to the high reactivity of 2-nitro-2-cyclohexenone (64) towards water or iodide ion and the product formed thereby being highly water soluble.

Alternative way of getting 64 from 69 could be via 71. Addition of thiophenol to 69 was expected to give 71 which then could be converted to 64 by hydrolysis followed by oxidative



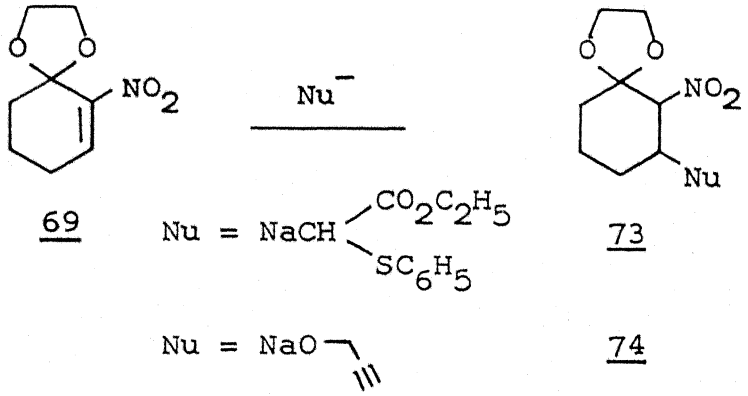
69 71 72 64

Scheme I.15

elimination (Scheme I.15). As expected, the reaction of 2-nitro-2-cyclohexenone acetal with thiophenol in the presence of catalytic amount of piperidine gave 71 in 88% yield. Its IR spectrum showed absorption at 1550 cm^{-1} (ν_{NO_2}) and its ^1H NMR spectrum showed absorptions at δ 1.35-2.4 (m, 6H), 3.2-3.55 (m, 1H, C<u>H</u>-SC_6H_5), 3.8-4.15 (m, 4H, acetal CH_2), 4.5 (d, J=6 Hz, 1H, C<u>H</u>-NO_2) and δ 7.25-7.7 (m, 5H aromatic). Surprisingly, the hydrolysis of 71 to get 72 also proved to be difficult, with NaI-BF_3.Et_2O in refluxing

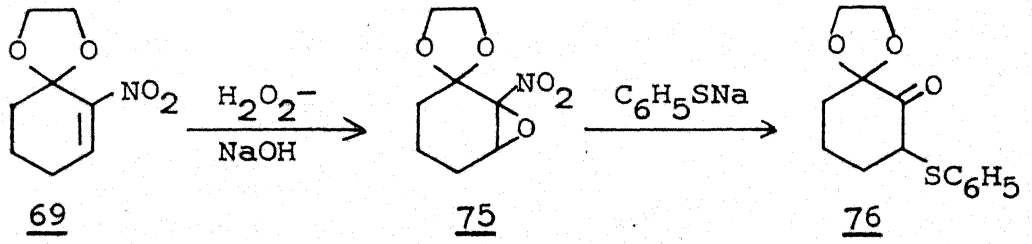
acetonitrile and with 5 % aqueous sulphuric acid. Under these conditions the starting material was recovered back.

In order to assess the reactions of 69 towards other nucleophiles, it was first reacted with carbanion of ethyl(phenylthio)-acetate to obtain compound 73 in 53 % yield. Similarly treatment of anion of propargyl alcohol with 69 gave 74 in 85 % yield. Once again the structures of these compounds 73 and 74 were assigned on the basis of IR, ^{1}H NMR and mass spectral data and elemental analysis (cf. experimental section).



Scheme I.16

Compound 69 not only undergoes Michael reaction but also can be epoxidised[42] using H_2O_2-NaOH. Further, the reaction of nitroepoxide 75 thus obtained, with sodium thiophenolate gave 76. IR spectrum of the compound 76 showed a strong absorption at



Scheme I.17

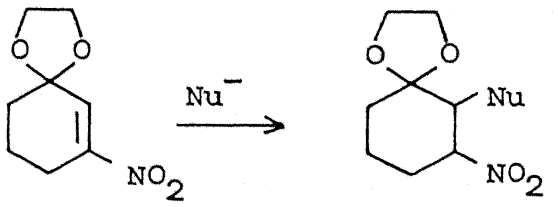
1725 cm^{-1} ($\nu_{C=O}$) and its ^1H NMR showed absorptions at δ 1.4-2.0 (m, 6H), 3.65-4.3 (m, 5H, acetal CH_2 and $C\underline{H}-SC_6H_5$), 7.1-7.6 (m, 5H, aromatic). These data confirm the structure assigned to 76.

Compounds obtained so far viz. 71, 73, 74 and 76 are highly functionalized derivatives of cyclohexane which have not been reported in the literature so far. Their further utility in organic synthesis is worth studying.

It was of interest to study the nucleophilic reactions on 3-nitro-2-cyclohexenone (31b) a complementary substrate to 64. Although, it has been described by Corey et al.[20] that compound 31b was a powerful dienophile in Diels-Alder reaction (vide supra), where the directional property of nitro group dominates over that of the keto group, no study, however, has been reported, to our knowledge, to test the behaviour of 31b as a Michael acceptor.

Hence, the present study was focussed on the addition of various nucleophiles such as sodium thiophenolate, carbanion of ethyl(phenylthio)acetate and diethyl sodiomalonate, to 31b. But the reactions were not at all clean, under various experimental conditions, giving a number of compounds as revealed by the tlc of the reaction mixtures. This may be due to the competitive addition of nucleophiles in 1,2 and 1,4 manner and the instability of products derived thereof under the experimental conditions. On the other hand nucleophilic additions on 37, gave clean addition products as expected based on the earlier experience of similar

additions on 69. The products 77, 78 and 79 of these additions are shown in Scheme I.18 , which were obtained by reacting 37 with thiophenol, ethyl (phenylthio)acetate and propargyl alcohol under basic conditions in 78 %, 61 % and 83 % yields respectively. Structures of these products were confirmed by their spectral data (cf. experimental section).



37

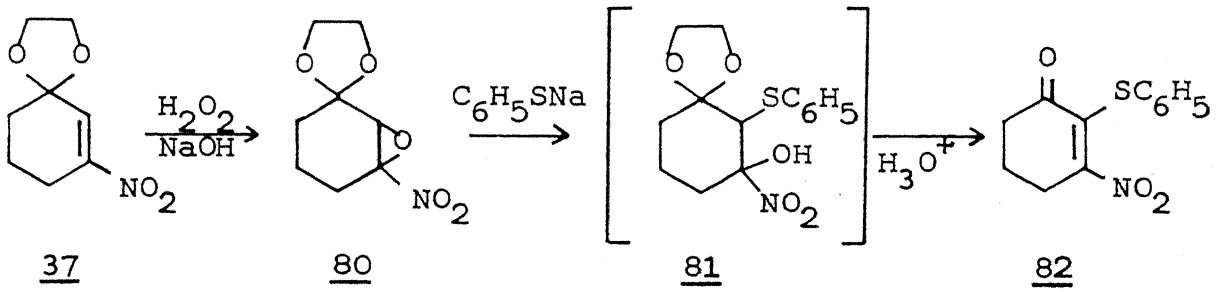
Nu = $NaSC_6H_5$ 77

= $NaCH(CO_2C_2H_5)(SC_6H_5)$ 78

= NaO— 79

Scheme I.18

Epoxidation of 37 to obtain 80 was also carried out in an analogous manner as described earlier (vide supra) for compound 69. However, interestingly reaction of 80 with sodium thiophenolate gave a product which indicated it to be 81 on the basis of its spectral data. However, during purification by thin layer

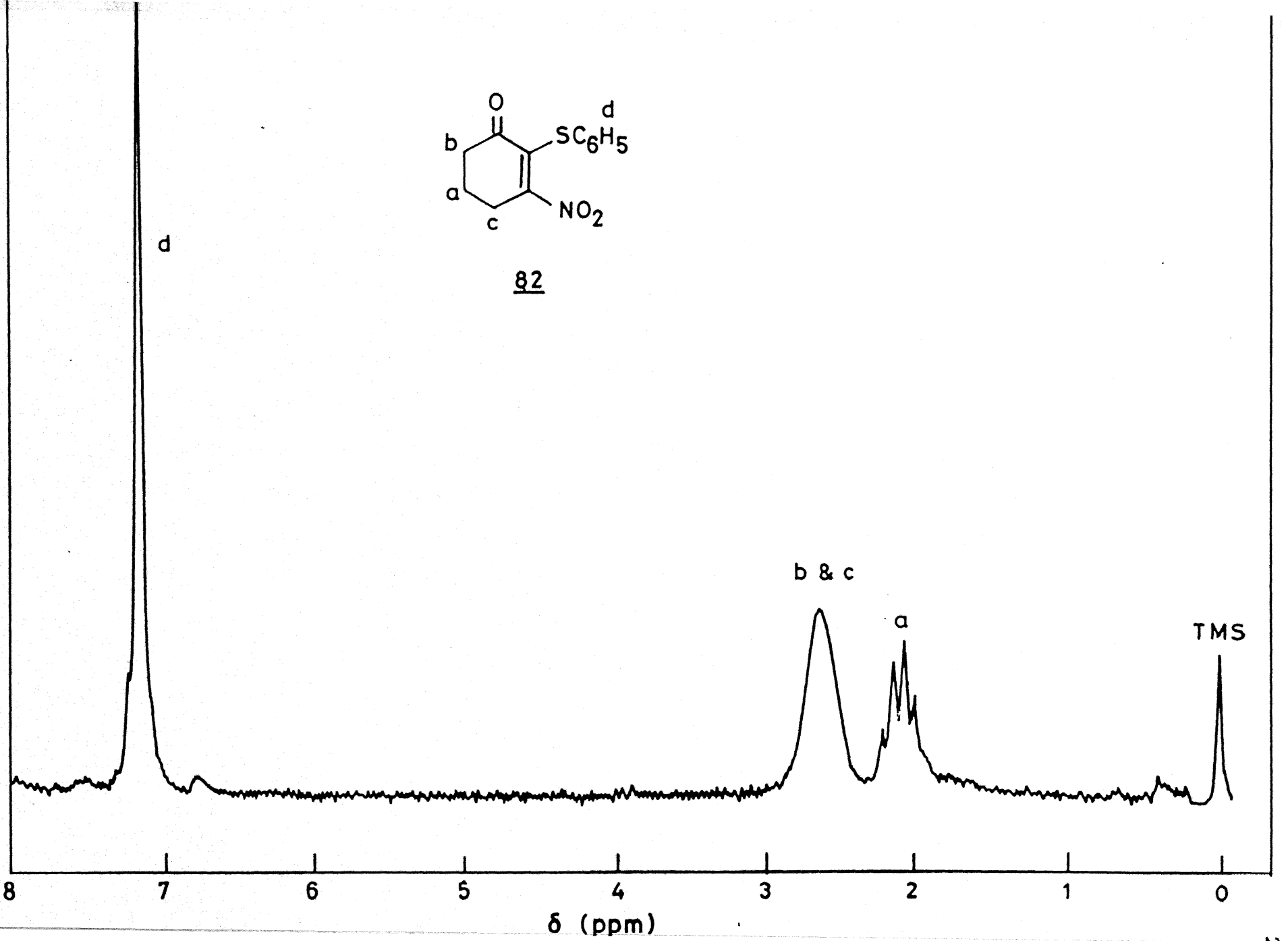


Scheme I.19

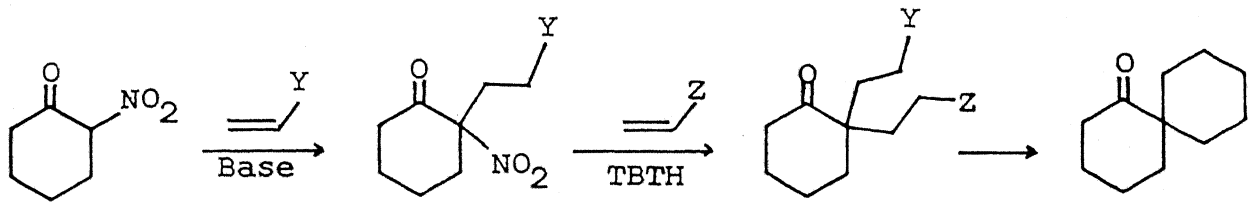
chromatography, it got converted into 82 partially. This could be due to the slight acidic nature of silica gel. Hence, the crude product of the reaction was treated with 5 % H_2SO_4 to obtain 82 in 43 % yield. Its spectral data confirm the structure 82. Thus, its IR spectrum showed absorption at 1650 cm^{-1} ($\nu_{C=O}$) and 1550 cm^{-1} (ν_{NO_2}). ^1H NMR spectrum showed absorptions at 1.9-2.25 (m, 2H, CH_2), 2.4-2.9 (m, 4H, allylic CH_2 and $COCH_2$), 7.2 (m, 5H, aromatic) (Fig. I.2).

Compound 79 (and also 74 obtained earlier) was of special interest to us, to convert it into useful α-methylene-ν-butyrolactone[43] by exploiting the chemistry of tertiary nitro compounds as sources of radical precursors.[29,44] This is described towards the end of this chapter.

Spirocyclic system is present in various natural products like spirovetivanes, acoranes and chamigrenes. It is, thus, important to develop methods for a general synthesis of spirocyclic compounds. One of the possible ways using radical chemistry from tertiary nitro compounds is shown in Scheme I.20. To test its

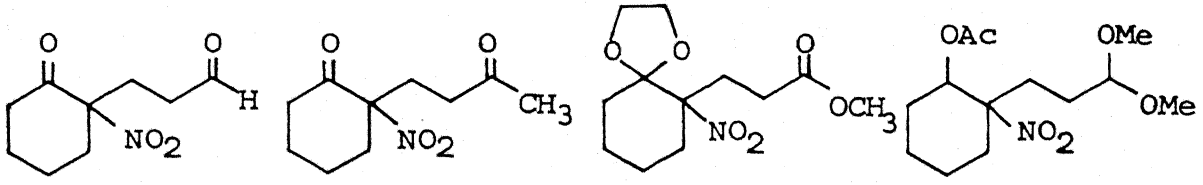

O
d
b
SC6H5
a
NO2
c
82
d
b & c
a
TMS
8
7
6
5
4
3
2
1
0
δ (ppm)

applicability, various Michael addition products 83, 84, 85 and 86



Scheme I.20

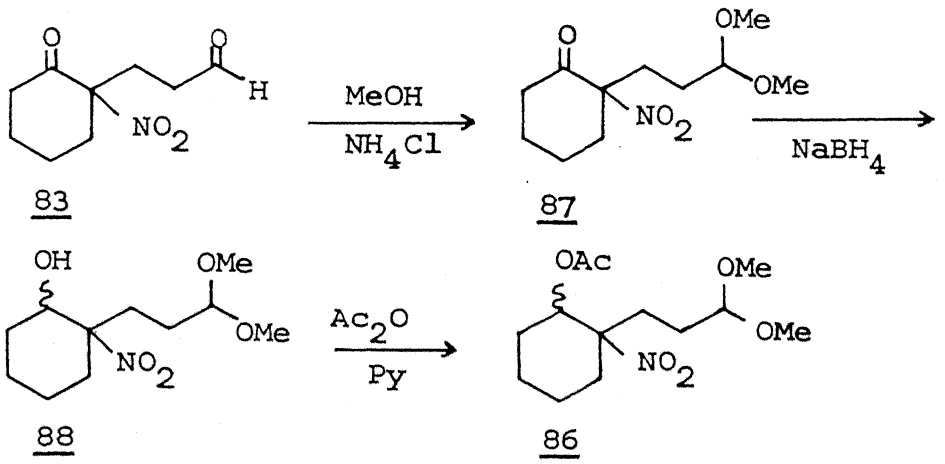
were synthesised starting from α-nitrocyclohexanone (10) and its acetal 67. Compounds 83 and 84 were synthesised from α-nitrocyclohexanone (10), following the literature procedure,[45,46] with



83 84 85 86

acrolein and methyl vinyl ketone in the presence of triphenylphosphine in 86% and 90% respectively. Compound 85 was prepared from nitroacetal 67 with methyl acrylate in the presence of Triton B.[38] Treatment of 83 with methanol in the presence of NH_4Cl gave 87.[47] Reduction of 87 with $NaBH_4$ in methanol gave 88 which was acetylated using acetic anhydride and pyridine to obtain 86 (Scheme I.21). ^1H NMR spectrum of 86 (homogeneous on tlc) showe

two multiplets at δ 5.37 and at δ 5.55 for C<u>H</u>-OAc and two triplets



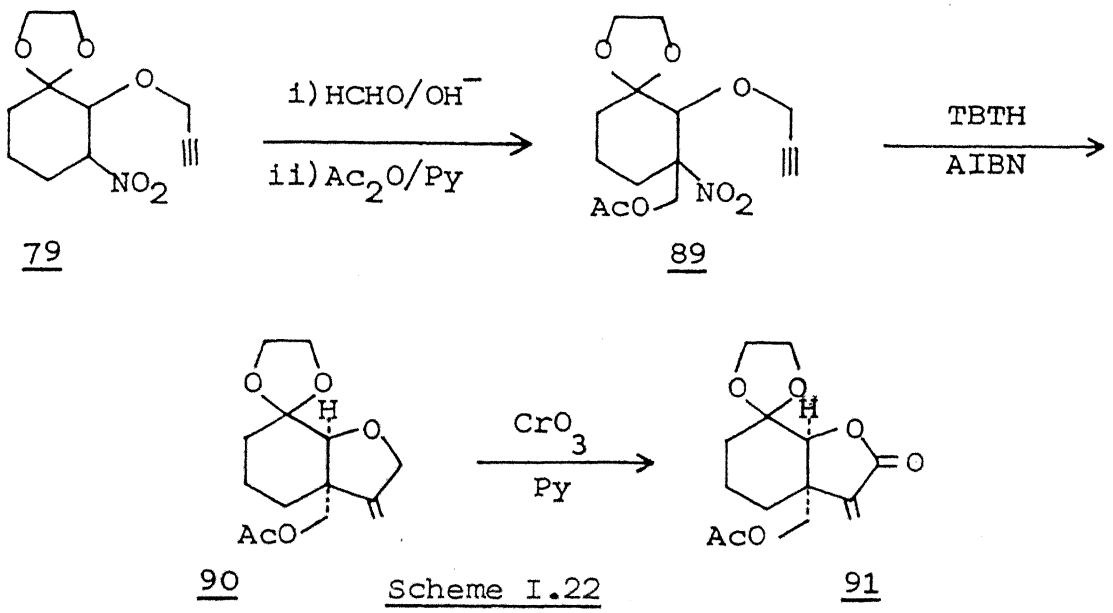
<u>83</u> <u>87</u> <u>88</u> <u>86</u>

Scheme I.21

at δ 4.02 and at δ 4.28 for C<u>H</u>$(OMe)_2$. From the integration of thes protons, it is evident that the acetate <u>86</u> is a 50:50 mixture of two isomers.

Treatment of these nitro compounds with acrylonitrile in the presence of TBTH gave a number of products which could not be purified to obtain any useful intermediate.

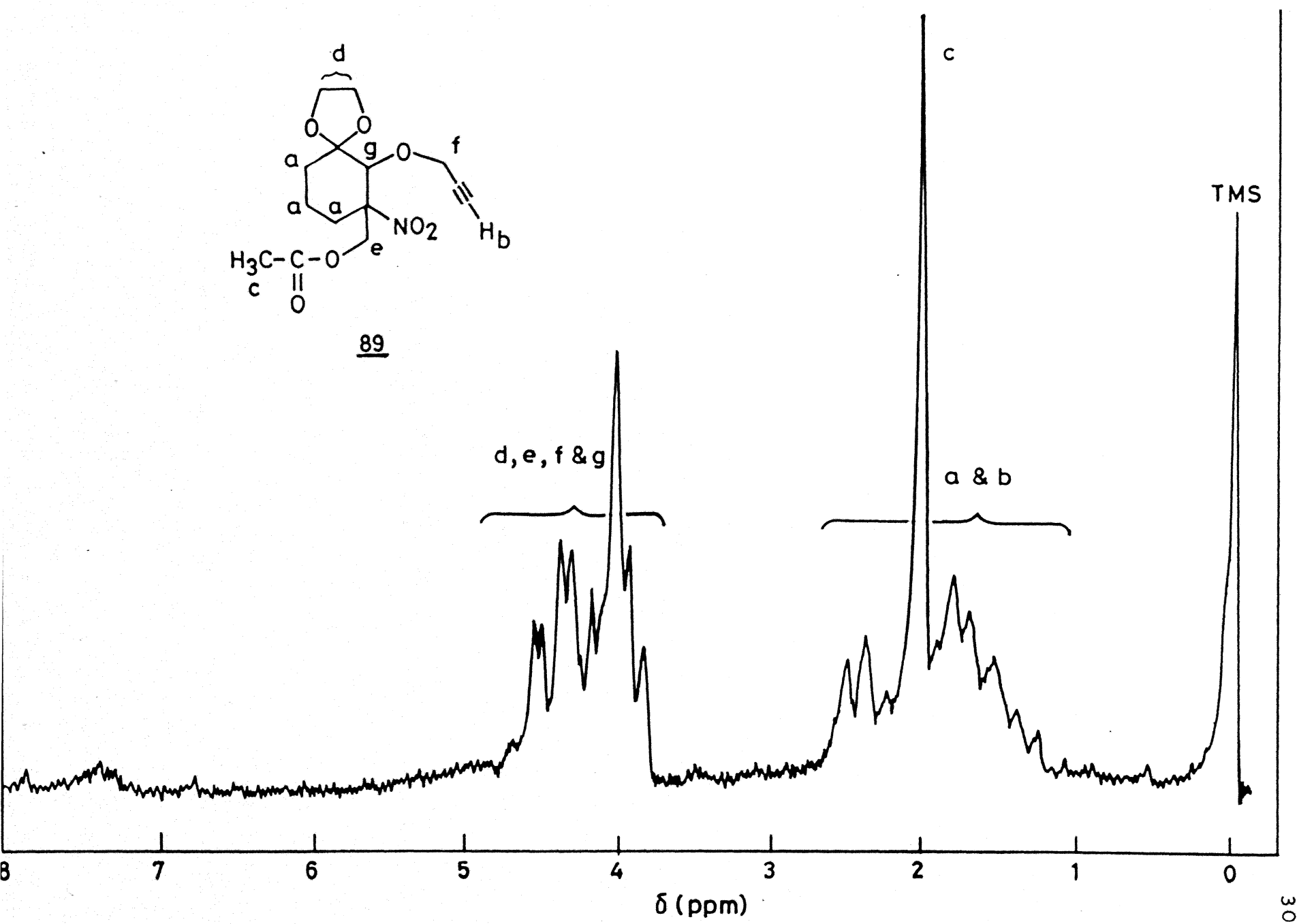
The failure to direct radical based intermolecular condensation reactions prompted us to look into some intramolecular react ions with nitrocompounds obtained in the earlier reactions. Thus compound <u>79</u> was converted into <u>91</u> by a sequence of reactions as shown in Scheme I.22.

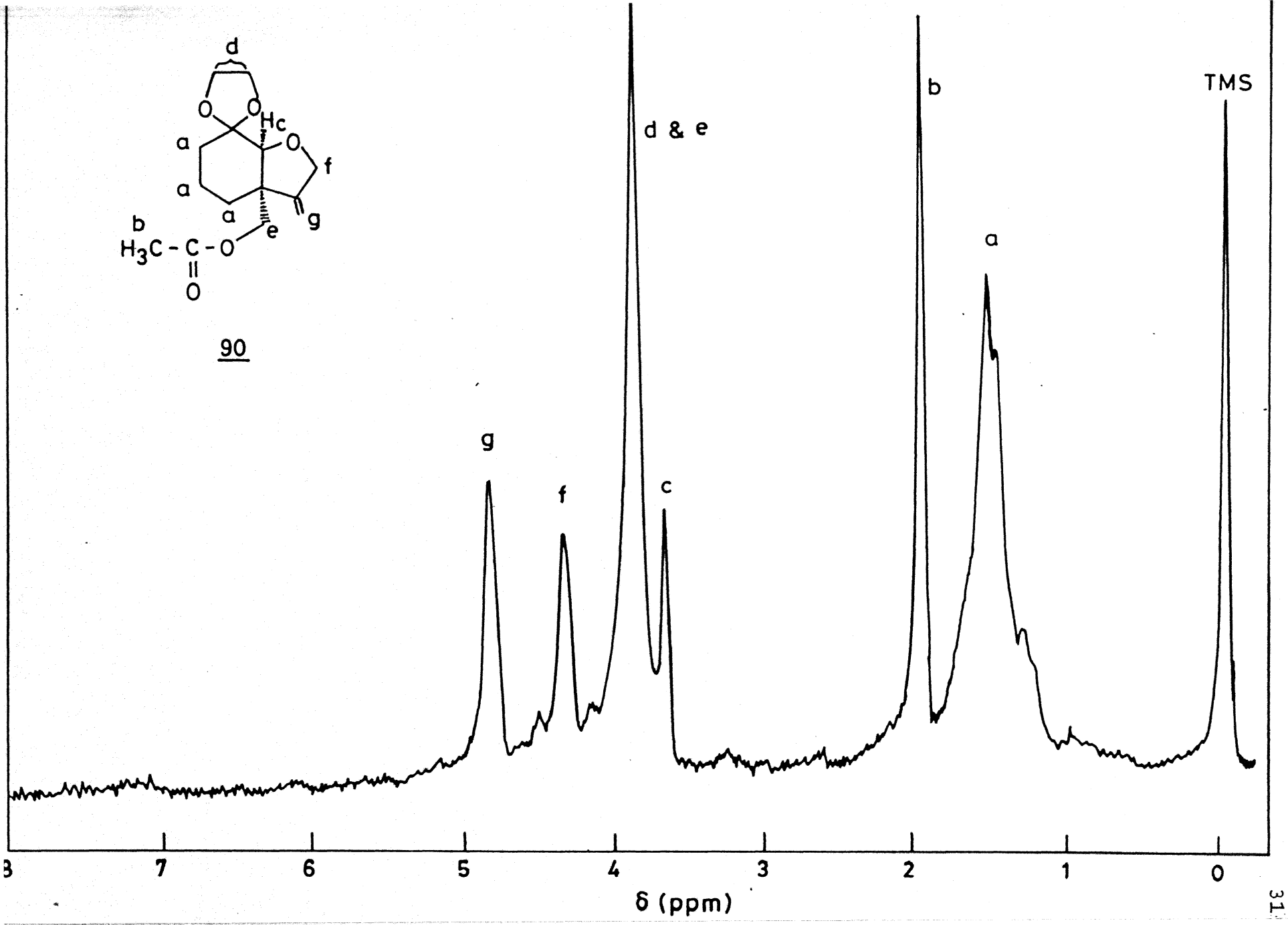


79 89 90 91

Scheme I.22

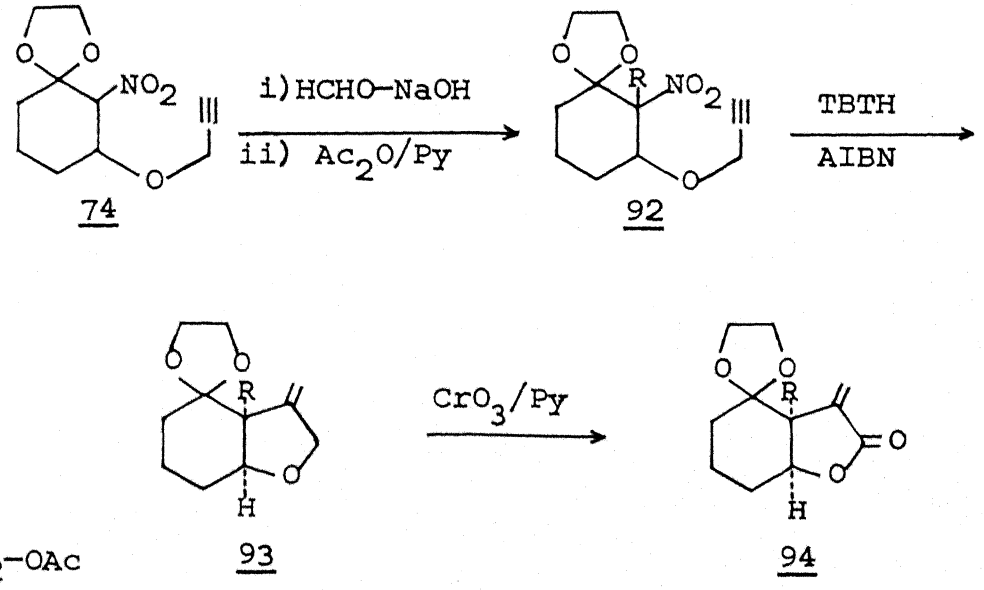
Reaction of compound 79 with HCHO in the presence of NaOH in isopropanol, followed by acetylation using acetic anhydride and pyridine gave 89.[31] IR spectrum of the compound 89 showed absorptions at 3280 cm^{-1} ($\nu_{C\equiv C-H}$), 2110 cm^{-1} ($\nu_{C\equiv C}$), 1740 cm^{-1} ($\nu_{C=O}$), 1540 cm^{-1} (ν_{NO_2}) and its ^1H NMR spectrum showed absorptions at δ 1.4-2.75 (m, 6H), 2.05 (s, 3H, $COCH_3$), 3.8-4.65 (m, 9H) (Fig.I.3). These data confirm the structure assigned to 89. Treatment of 89 with TBTH and 2,2'-azobisisobutyronitrile (AIBN) in refluxing benzene for 5 h gave 90 in 51% yield whose ^1H NMR spectrum showed absorptions at δ 1.15-1.85 (m, 6H), 2.0 (s, 3H, $COCH_3$), 3.7 (s, 1H, $CH-O-CH_2$), 3.8-4.1 (m, 6H, acetal CH_2 and CH_2-OAc), 4.4 (s, 2H, $CH-O-CH_2$), 4.8-4.95 (m, 2H, olefinic) (Fig. I.4). Whereas its mass spectrum showed a peak at 195 (M^+-CH_2-OAc). Oxidation[48] of 90 with chromium trioxide-pyridine in CH_2Cl_2 gave the desired lactone 91 in 65% yield. The spectral properties of this compound as shown below, confirm its assigned structure. IR spectrum: 1770 cm^{-1} ($\nu_{C=O}$)


d
O
O
g
O
f
a
a
a
NO2
Hb
e
H3C-C-O
c
O
89
c
TMS
d, e, f & g
a & b
8
7
6
5
4
3
2
1
0
δ (ppm)


d
O
O
Hc
O
a
a
a
f
g
e
b
H3C - C - O
O
90
g
f
c
d & e
b
a
TMS
8
7
6
5
4
3
2
1
0
δ (ppm)

1740 cm^{-1} ($\nu_{C=O}$) ^1H NMR spectrum: δ 1.55–2.0 (m, 6H, CH_2) 2.05 (s, 3H, $COCH_3$), 3.85–4.3 (m 6H, acetal CH_2 and $\underline{CH}_2$–OAc), 4.4 (s, 1H, $\underline{CH}$–O–CO), 5.55 (s, 1H, olefinic), 6.4 (s, 1H, olefinic) (Fig. I.5). Mass spectrum, m/e: 282 (M^+).

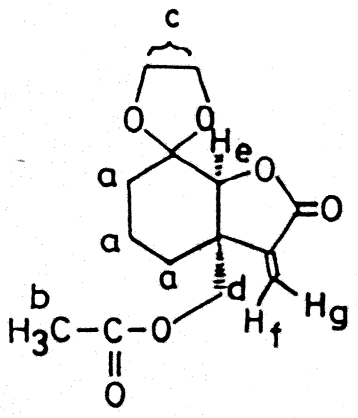
Similar sequence of reactions with 74 could have led to the product 94 which is complementary to 91. However, initial failure to obtain 92 with HCHO–KOH followed by acetylation did not permit us to pursue it further. This failure could be attributed to steric factors.



74 92 93 94

Scheme I.23

The above studies with a variety of nitroolefins and tertiary nitro compounds lead to the formation of useful intermediates using Michael reactions and radical based reactions respectively are expected to broaden the horizon of such chemistry.



91

I.3 Experimental

All the melting points are uncorrected and were taken on Fischer-Johns melting point apparatus.

Infrared (IR) spectra were recorded on Perkin-Elmer model 377, 580 and 1320 spectrometers and are reported in wave numbers.

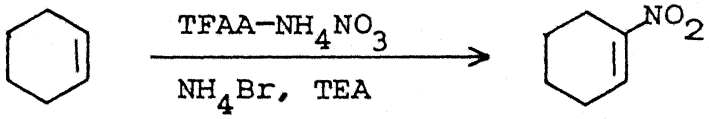
Proton magnetic resonance (^{1}H NMR) spectra were recorded on Bruker WP-80 (80 MHz), EM 390 (90 MHz), Varian HA 100 (100 MHz) and Jeol PMX 60 (60 MHz) instruments. Chemical shifts are reported in parts per million (ppm) downfield from internal reference tetramethylsilane (δ). Multiplicity is indicated using the following abbreviations: s (singlet), br (broad), d (doublet), t (triplet), q (quartet) and m (multiplet). Coupling constants (J) are reported wherever necessary and are expressed in Hz.

Mass spectra were recorded on Jeol JMS-300D Mass spectrometer at 70 eV. The elemental analyses were carried out in Coleman automatic carbon, hydrogen and nitrogen analysers.

Commercial grade solvents were distilled prior to use. Chloroform used in the reactions was shaken five times with about half of its volume of water, then dried over anhydrous calcium chloride for 24 h and distilled over P_2O_5. Finally it was stored over Type 5A molecular sieves. Methylene chloride was distilled over P_2O_5. Benzene and toluene were first treated with anhydrous calcium chloride, filtered, distilled and stored over sodium wire.

Tetrahydrofuran was dried by storing over KOH pellets for more than 24 h, decanting, refluxing and distilling successively over sodium wire and lithium aluminium hydride and finally storing over fresh sodium wire. Diethyl ether was dried by storing over $CaCl_2$ for 24 h, decanting, refluxing and distilling over sodium wire. Finally it was distilled over lithium aluminium hydride. Acetonitrile was dried by first storing over anhydrous $CaCl_2$ for at least 24 h. It was then distilled over P_2O_5 and stored over Type 4A molecular sieves.

Preparation of 1-nitrocyclohexene (12)



12

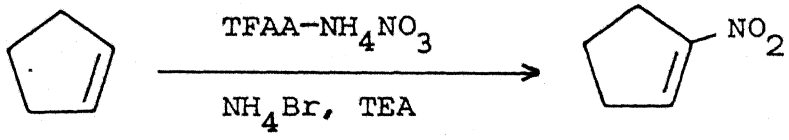
To a stirred suspension of ammonium nitrate (320 mg, 4 mmol) in chloroform at 0°C was added trifluoroacetic anhydride (0.56 mL, 4 mmol). The resultant mixture was stirred for 15 min then ammonium bromide (784 mg, 8 mmol) followed by cyclohexene (164 mg, 2 mmol) were added to it and stirring continued for 8 h. The reaction mixture was then diluted with water (10 mL), neutralized with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 (3 x 10 mL) and concentrated to about 2 mL. Triethylamine (0.35 mL, 2.5 mmol) was added to it and stirred for 1 h at room temperature. The resulting mixture was diluted with water (10 mL), extracted with CH_2Cl_2

(3 x 10 mL), washed successively with 5 % HCl (10 mL), water (10 mL), brine (10 mL) and then dried over anhydrous sodium sulphate. After evaporation of the solvent, crude product was purified by distillation. Yield 165 mg, (65%). b.p. 75-77°C/2 mm (lit.[8] b.p. 73°C/2 mm).

IR spectrum ν_{max}(neat): 1510 (NO_2) and 1335 (NO_2) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.35-2.00 (m, 4H, satd. CH_2), 2.15-2.75 (m, 4H, allylic CH_2) and 7.34 (m, 1H, vinylic).

Preparation of 1-nitrocyclopentene (61)



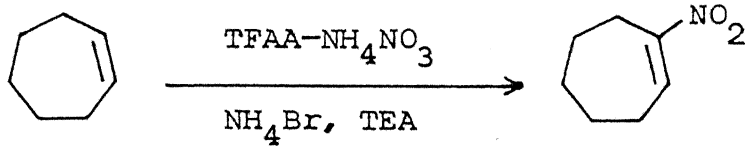
61

Following the above described procedure, the reaction of cyclopentene (136 mg, 2 mmol) with TFAA (0.56 mL, 4 mmol), ammonium nitrate (320 mg, 4 mmol), and ammonium bromide (784 mg, 8 mmol) in $CHCl_3$ at 0°C for 6 h, followed by treatment with triethylamine (0.35 mL, 2.5 mmol) gave a crude product which was purified by column chromatography. Eluent: Pet. ether:ether (90:10). Yield 113 mg (50%).

IR spectrum ν_{max}(neat): 1515 (NO_2), 1335 (NO_2) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 6.97-7.07 (m, 1H, vinylic).

Preparation of 1-nitrocycloheptene (14)



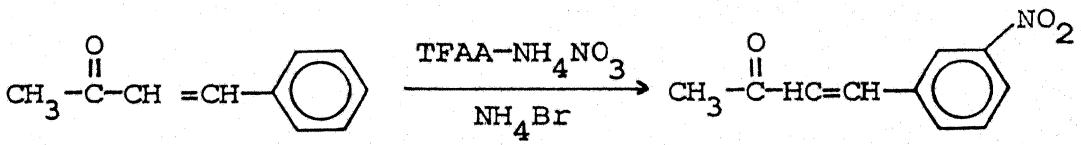
14

The reaction was carried out following the above described procedure. The reaction of cycloheptene (200 mg, 2.08 mmol) with TFAA (0.59 mL, 4.16 mmol), ammonium nitrate (330 mg, 4.16 mmol) and ammonium bromide (815 mg, 8.32 mmol) in $CHCl_3$ at 0°C for 10 h, followed by treatment with triethylamine (0.36 mL, 2.6 mmol) gave a crude product which was purified by column chromatography. Eluent: Pet. ether:ether (90:10). Yield 185 mg (63%).

IR spectrum ν_{max}(neat): 1515 (NO_2), 1335 (NO_2) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.8 (m, 6H, satd. CH_2), 2.4 (m, 2H, allylic CH_2), 2.9 (m, 2H, allylic CH_2), 7.47 (t, 1H, J=7 Hz, vinylic).

Preparation of 4 (3-nitrophenyl)but-3-en-2-one (66)



65 66

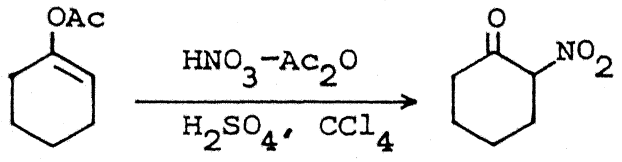
The reaction of 65 (100 mg, 0.685 mmol) with TFAA (0.19 mL, 1.37 mmol), ammonium nitrate (110 mg, 1.37 mmol) and ammonium

bromide (268 mg, 2.74 mmol) in $CHCl_3$ at 0°C for 5 h gave a crude product which was purified by preparative thin layer chromatography to obtain 66. Yield 50 mg (38%).

IR spectrum ν_{max} ($CHCl_3$): 1680 (C=O), 1610 (C=C), 1530 (NO_2), 1350 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 2.4 (s, 3H, methyl), 6.7 (d, 1H, J=7.5 Hz, COCH=CH), 7.3-8.5 (m, 5H, aromatic and COCH=CH).

Preparation of 2-nitrocyclohexanone (10)

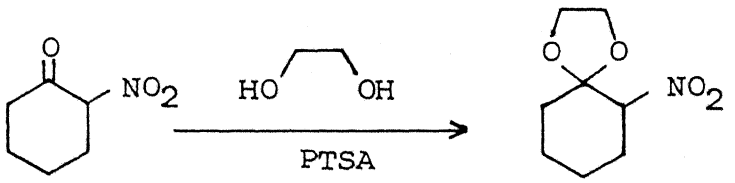


95 10

A mixture of concentrated nitric acid (5 mL, 0.079 mol) and glacial acetic acid (3.6 mL) was added in the course of 30 min to a mixture of 1-acetoxy-1-cyclohexene (95) (10 g, 0.072 mol), acetic anhydride (22 mL), carbontetrachloride (18 mL) and concentrated sulfuric acid (one drop) at 15-25°C with cooling. The mixture was then stirred for 2 h while cooling with ice, after which water (1.5 mL) was added and stirred for 15 min at room temperature. Acetic acid was removed as completely as possible in vacuo at 40°C bath temperature, the residue was dissolved in ether (100 mL) and it was washed with water (2 x 20 mL). After drying over anhydrous sodium sulphate, the solvent was distilled and the product was purified by column chromatography. Eluent: Pet.ether: ether (85:15)

to give 10. Yield 8 g (78%). m.p. 30–32°C (lit.[49] m.p. 32°C).

Preparation of 2-nitrocyclohexanone acetal (67)



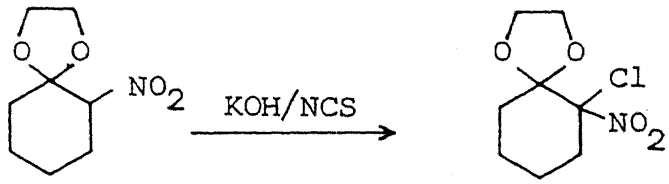
10 67

A mixture of 2-nitrocyclohexanone (10) (2 g, 14 mmol), ethylene glycol (2.65 mL, 48 mmol) and p-toluenesulphonic acid (0.05 g) in dry toluene (20 mL) was heated under reflux for 4 h with azeotropic removal of water using Dean-Stark apparatus. After cooling to room temperature, the reaction mixture was washed successively with 10% $NaHCO_3$ (20 mL), water (25 mL), brine (10 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a gum which was purified through a silica gel column by eluting with benzene. Yield 1.8 g (69%). b.p. 125–130°C/5 mm (lit.[38] b.p. 125–127°C/7 mm).

IR spectrum ν_{max} ($CHCl_3$): 1550 (NO_2), 1375 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.2–2.55 (m, 8H, CH_2), 3.95 (s, 4H, acetal CH_2), 4.35–4.7 (m, 1H, $\underline{CH}-NO_2$).

Preparation of 2-chloro-2-nitrocyclohexanone acetal (68)



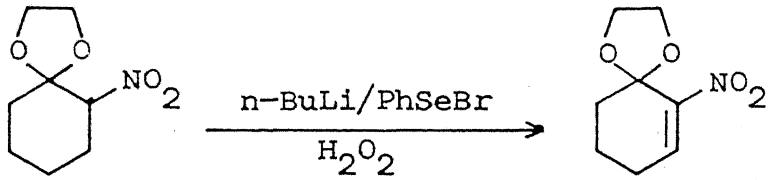
67 68

To a stirred solution of potassium hydroxide (60 mg, 1.07 mmol) in dioxan-water (70:30, 4 mL) was added a solution of 2-nitrocyclohexanone acetal (67) (200 mg, 1.07 mmol) in 1 mL of dioxan under nitrogen atmosphere. After stirring for 15 min at room temperature N-chlorosuccinimide (NCS) (174 mg, 1.3 mmol) was added all at once. The reaction was exothermic and the yellow nitronate solution bleaches instantly. Stirring was continued at room temperature for 1 h. The solvent was removed under reduced pressure, the residue was diluted with water (5 mL) extracted with CH_2Cl_2 (3 x 20 mL). The combined extracts were washed with water (2 x 20 mL), brine (10 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure gave a crude product which was recrystallized from methanol. Yield 120 mg (51%), m.p. 74-76°C (lit.[39] m.p. 78-80°C).

IR spectrum ν_{max} (KBr): 1550 (NO_2), 1355 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.5-1.95 (m, 6H, CH_2), 2.0-2.45 (m, 1H, $\underline{CH}-\overset{|}{C}-NO_2$), 2.6-3.05 (m, 1H, $\underline{CH}-\overset{|}{C}-NO_2$), 3.95 (s, 4H, acetal CH_2).

Preparation of 2-nitro-2-cyclohexenone acetal (69)



67 69

To a stirred solution of 2-nitrocyclohexanone acetal (67) (374 mg, 2 mmol) in THF (5 mL) at 0°C was added n-BuLi (1.75 mL, 15% solution in hexane, 4 mmol). After stirring for 30 min, a solution of benzeneselenyl bromide in anhydrous THF [prepared from diphenyl diselenide (662 mg, 4.2 mmol) and bromine (0.1 mL, 4.2 mmol)] was added during 10 min. After 1 h, 30% H_2O_2 (2 mL) was added and the resultant mixture was stirred at room temperature for 4 h. It was then diluted with water (20 mL) and extracted with ether (3 x 25 mL). The organic layer was washed with water (2 x 20 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude product which was purified by column chromatography, [elueted with pet. ether:ether (90:10)]. Yield 190 mg (51%).

IR spectrum ν_{max}(neat): 1510 (NO_2), 1340 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.8 (m, 4H, satd. CH_2), 2.2-2.55 (m, 2H, allylic CH_2), 3.85-4.35 (m, 4H, acetal CH_2), 7.2 (m, 1H, vinylic).

Mass spectrum, m/e (rel.int.): 185 (6, M^+), 157 (100, $M^+-CH_2=CH_2$), 139 (10, M^+-NO_2), 111 (13, M^+-NO_2, $-CH_2=CH_2$), 97 (63).

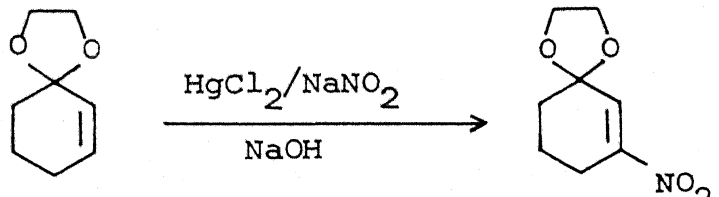
Anal. Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.95; N, 7.57. Found C, 51.93; H, 6.02; N, 7.51.

Note: Nitroselenide 70 was isolated from the reaction mixture in 62% yield whose spectral details are given below.

IR spectrum ν_{max}(neat): 1530 (NO_2), 1345 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.3–2.7 (m, 8H, CH_2), 3.85–4.2 (m, 4H, acetal CH_2), 7.15–7.6 (m, 5H, aromatic).

Preparation of 3-nitro-2-cyclohexenone acetal (37)



36 37

To a stirred solution of sodium nitrite (828 mg, 12 mmol) in water (3 mL) was added mercuric chloride (1.630 g, 6 mmol) and 2-cyclohexenone acetal (36) (840 mg, 6 mmol) at room temperature. After stirring for 1.5 h, the solid nitromercurial was filtered and washed with water (10 mL). The crude nitromercurial was dissolved in CH_2Cl_2 (5 mL) treated with aqueous sodium hydroxide (2.4 mL, 2.5N, 6 mmol) and stirred at room temperature for 15 min. The reaction mixture was filtered through celite (to remove metallic mercury) and washed with CH_2Cl_2 (50 mL). The organic layer was washed with water (2 x 10 mL) brine (10 mL) and dried over anhydrous

sodium sulphate. Evaporation of the solvent gave a crude product which was purified by distillation. Yield 380 mg (80%), b.p. 120°C/1 mm.

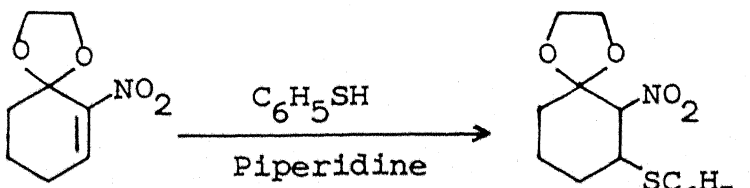
IR spectrum ν_{max}(neat): 1510 (NO_2), 1330 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.62-2.1 (m, 4H, CH_2), 2.56 (m, 2H, allylic CH_2), 3.94 (s, 4H, acetal CH_2), 6.7 (s, 1H, vinylic).

Mass spectrum, m/e (rel.int.): 185 (10, M^+), 154 (39, M^+-NO), 138 (40, M^+-NO_2), 111 (100, M^+-NO_2, $-CH_2=CH_2$).

Anal. Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.95; N, 7.57. Found C, 51.83, H, 6.08; N, 7.60.

Preparation of 2-nitro-3-phenylthiocyclohexanone acetal (71)



69 71

To a mixture of 2-nitro-2-cyclohexenone acetal (69) (50 mg, 0.27 mmol) and thiophenol (0.03 mL, 0.27 mmol) in CH_2Cl_2 (2 mL) at 0°C under nitrogen atmosphere was added a drop of piperidine and stirred for 1 h. After addition of water (5 mL), the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL), washed with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude product which was purified

by preparative thin layer chromatography using silica gel to obtain a thick liquid. Yield 70 mg (88%).

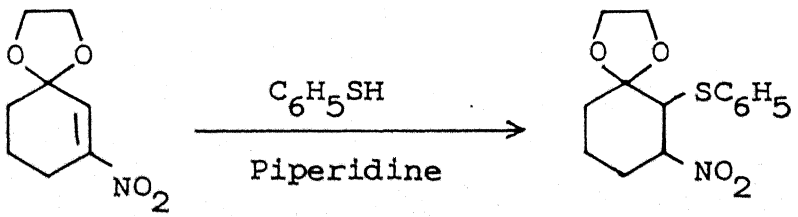
IR spectrum ν_{max}(neat): 1550 (NO_2), 1370 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.35–2.4 (m, 6H, CH_2), 3.2–3.55 (m, 1H, $C\underline{H}-SC_6H_5$), 3.8–4.15 (m, 4H, acetal CH_2), 4.5 (d, 1H, J=6 Hz $C\underline{H}-NO_2$), 7.25–7.7 (m, 5H, aromatic).

Mass spectrum, m/e (rel.int.): 295 (19, M^+), 186 (100, $M^+-SC_6H_5$), 99 (45).

Anal. Calcd for $C_{14}H_{17}NSO_2$: C, 56.95; H, 5.76; N, 4.75. Found C, 56.98; H, 5.82; N, 4.70.

Preparation of 3-nitro-2-phenylthio cyclohexanone acetal (77)



37 77

A mixture of 3-nitro-2-cyclohexenone acetal (37) (925 mg, 5 mmol), thiophenol (660 mg, 6 mmol) and a drop of piperidine was refluxed in benzene (10 mL) for 15 h. After cooling to room temperature, it was diluted with water (10 mL), extracted with ether (3 x 20 mL), washed with water (2 x 10 mL), brine (10 mL) and dried over anhydrous sodium sulphate. The crude product was recrystallized from $CHCl_3$-pet.ether. Yield 1.1 g (78%), m.p. 114°C.

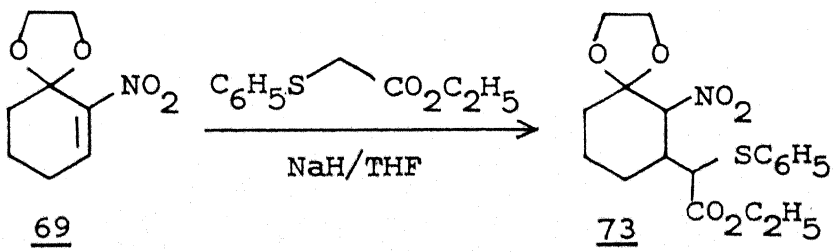
IR spectrum ν_{max}: 1545 (NO_2), 1360 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.25–2.15 (m, 5H, satd. CH_2), 2.2–2.5 (m, 1H, $\underline{CH}-\overset{|}{\underset{|}{C}}-NO_2$), 3.5 (d, 1H, J=6 Hz, $\underline{CH}-SC_6H_5$), 3.88–4.44 (m, 4H, acetal CH_2), 4.6–4.72 (m, 1H, $\underline{CH}-NO_2$), 7.1–7.5 (m, 5H, aromatic).

Mass spectrum, m/e (rel.int.): 295 (15, M^+), 249 (100, M^+-NO_2), 139 (80, M^+-NO_2, $-SC_6H_5$).

Anal. Calcd for $C_{14}H_{17}NSO_2$: C, 56.95, H, 5.74; N, 4.75. Found C, 56.90; H, 5.85; N, 4.80.

Preparation of 2-nitro-3 (α-carboethoxy, α-phenylthio methyl)-cyclohexanone acetal (73)

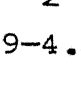


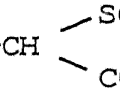
69 73

Ethyl (phenylthio)acetate (64 mg, 0.33 mmol) in THF was added to a suspension of sodium hydride (18 mg, 50% suspension in oil, 0.37 mmol) in THF at 0°C. The resultant mixture was stirred at room temperature for 30 min. 2-nitro-2-cyclohexenone acetal (69) (50 mg, 0.27 mmol) in THF was added dropwise with ice-water cooling and stirred for another 30 min. Then, it was neutralized with saturated NH_4Cl, extracted with CH_2Cl_2 (3 x 10 mL), washed with

water (10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude product which was purified by preparative thin layer chromatography to obtain a thick liquid. Yield 55 mg (53%).

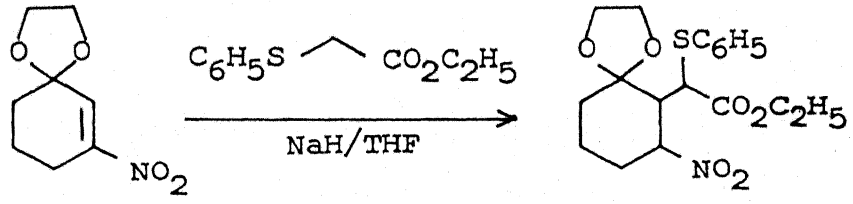
IR spectrum ν_{max}(neat): 1725 (C=O), 1545 (NO_2) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.2 (t, 3H, J=7.5 Hz, methyl), 1.45-2.15 (m, 6H, satd. CH_2), 2.4 (m, 1H, $CH-\underset{|}{\overset{|}{C}}-NO_2$), 3.2-3.65 (m, 2H, $\underline{CH}-\underline{CH}$ ), 3.9-4.5 (m, 7H, acetal CH_2, $O\underline{CH_2}CH_3$ and $\underline{CH}-NO_2$).

Mass spectrum, m/e (rel.int.): 381 (74, M^+), 335 (10, M^+-NO_2) 225 (10, M^+-NO_2, $-SC_6H_5$), 185 (38, M^+-CH ), 99 (100).

Anal. Calcd for $C_{18}H_{23}NSO_6$: C, 56.69; H, 6.04; N, 3.67; Found: C, 56.73; H, 5.97; N, 3.59.

Preparation of 3-nitro-2(α-carboethoxy, α-phenylthio methyl)-cyclohexanone acetal (78)

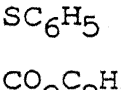
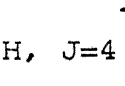


37 78

Following the above described procedure for 73, the reaction of 3-nitro-2-cyclohexenone acetal (37) (185 mg, 1 mmol) with ethyl (phenylthio)acetate (225 mg, 1.3 mmol) and NaH (64 mg, 1.3 mmol)

for 2 h at room temperature gave 78 as a thick liquid. Yield 234 mg (61%).

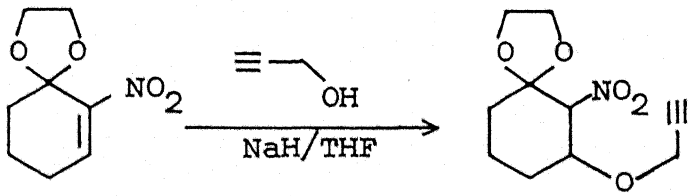
IR spectrum ν_{max}(neat): 1725 (C=O), 1545 (NO_2).

^{1}H NMR spectrum (CCl_4 + $CDCl_3$): δ 1.25 (t, 3H, J=7.5 Hz, methyl), 1.5-2.7 (m, 6H, satd. CH_2), 3.35 (dd, 1H, J=12 Hz, 4.5 Hz, $\underline{CH}$-CH()), 3.75 (d, 1H, J=4.5 Hz, $\underline{CH}$()), 3.85-4.45 (m, 7H, acetal CH_2, $CO\underline{CH_2}CH_3$ and $\underline{CH}$-NO_2).

Mass spectrum m/e (rel.int.): 381 (50, M^+), 335 (57, M^+-NO_2), 272 (40, $M^+-SC_6H_5$), 99 (100).

Anal. Calcd for $C_{18}H_{23}NSO_6$: C, 56.69; H, 6.04; N, 3.67; Found: C, 56.64; H, 6.10; N, 3.75.

Preparation of 2-nitro-3-propargyloxycyclohexanone acetal (74)



69 74

To a stirred suspension of NaH (16 mg, 50% dispersion in oil, 0.33 mmol) in 3 mL of THF was added propargyl alcohol (18 mg, 0.32 mmol) at 0°C and the stirring was continued till evolution of gas ceased (~15 min). Then, 2-nitro-2-cyclohexenone acetal, (69), (50 mg, 0.27 mmol) in THF was added to the reaction mixture and the resultant mixture was stirred for another 15 min. It was

poured into ice-cold water (10 mL), neutralized with sat. NH_4Cl solution, extracted with ether (3 x 15 mL), washed with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulphate. The crude product obtained after evaporating the solvent, was purified by preparative thin layer chromatography to obtain 74 as a thick oil. Yield 55 mg (85%).

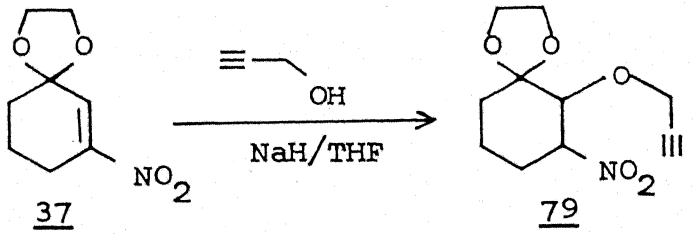
IR spectrum ν_{max}(neat): 3270 (C≡C-H), 2110 (C≡C), 1545 (NO_2), 1365 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4 + $CDCl_3$): δ 1.3-2.2 (m, 6H, satd. CH_2), 2.45 (s, 1H, C≡C-H), 3.9-4.55 (m, 7H, acetal CH_2 and $CH-O-CH_2$), 4.9 (d, 1H, J=6 Hz, $CH-NO_2$).

Mass spectrum m/e (rel.int.): 195 (8, M^+-NO_2), 186 (42, $M^+-OCH_2-C\equiv CH$), 123 (80), 99 (100).

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.22; N, 5.81. Found: C, 54.85; H, 6.28; N, 5.87.

Preparation of 3-nitro-2-propargyloxycyclohexanone acetal (79)



37 79

The reaction was carried out following the above described procedure for 74. The reaction of 3-nitro-2-cyclohexenone acetal (37) (925 mg, 5 mmol) with propargyl alcohol (340 mg, 6 mmol) and

NaH (300 mg, 6 mmol) in THF at 0° for 30 min. gave 79 which was purified by column chromatography. Yield 1.0 g (83%).

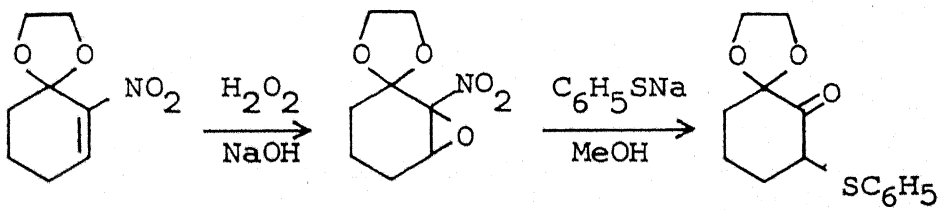
IR spectrum ν_{max}(neat): 3280 (C≡C-H), 2110 (C≡C, 1540(NO_2), 1370 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): 1.3-2.25 (m, 6H, satd. CH_2), 2.35 (s, 1H, C≡C-H), 3.85-4.7 (m, 8H, acetal CH_2, C<u>H</u>-O-C<u>H</u>$_2$ and C<u>H</u>-NO_2).

Mass spectrum, m/e (rel.int.): 195 (100, M^+-NO_2), 139 (11, M^+-NO_2, $-OCH_2-C{\equiv}C-H$), 99 (76).

Anal. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.22; N, 5.81; Found: C, 54.70; H, 6.28; N, 5.76.

Preparation of 2-keto-3-phenylthiocyclohexanone acetal (76)



69 75 76

To a stirred solution of 2-nitro-2-cyclohexanone acetal (69) (50mg, 0.27 mmol) in methanol containing 30% H_2O_2 (0.06 mL, 0.54 mmol) at $5^{\circ}C$ was added aqueous sodium hydroxide (0.07 mL, 2N, 0.14 mmol) rapidly. Stirring was continued at the same temperature for additional 10 min (turbidity develops during this time), then the reaction mixture was extracted with ether (3 x 15 mL),

washed with water (10 mL), brine (5 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent under reduced pressure gave a crude product. This, without further purification, was treated with sodium thiophenolate [prepared *in situ* from thiophenol (30 mg, 0.27 mmol) and sodium (6 mg, 0.27 mmol)] in methanol at 0°C. The resultant mixture was stirred for further 2 h, after which water (10 mL) was added, extracted with CH_2Cl_2 (3 x 15 mL), washed with water (10 mL), brine (5 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude product which was purified by the preparative thin layer chromatography [eluent, benzene: acetone (95:5)] to obtain a thick oil. Yield 60 mg (47%).

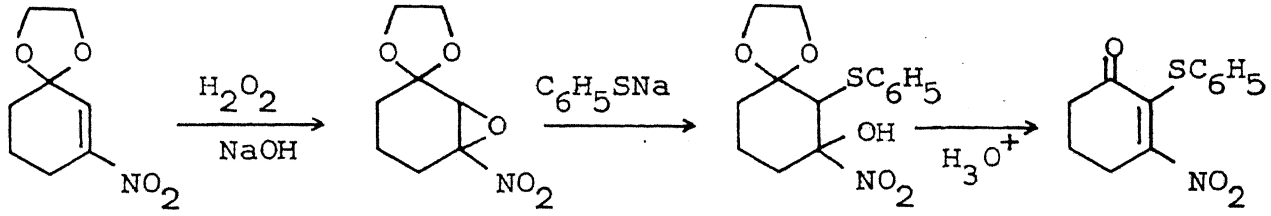
IR spectrum ν_{max}(neat): 1725 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.4-2.0 (m, 6H, satd. CH_2), 3.65-4.3 (m, 5H, acetal CH_2 and $C\underline{H}-SC_6H_5$), 7.1-7.6 (m, 5H, aromatic).

Mass spectrum m/e (rel.int): 264 (3, M^+), 235 (30), 155 (5, $M^+-SC_6H_5$), 99 (100).

Anal. Calcd for $C_{14}H_{16}SO_3$: C, 63.64; H, 6.06. Found: C,63.70; H, 6.12.

Preparation of 3-nitro-2-phenylthio-2-cyclohexenone (82)



The reaction was carried out following the above described procedure for 76. The reaction of 3-nitro-2-cyclohexenone acetal (37) (185 mg, 1 mmol) 30 % H_2O_2 (0.23 mL, 2 mmol) and NaOH in MeOH at 0^o for 10 min gave 80. This on further treatment with sodium thiophenolate [prepared from thiophenol (110 mg, 1 mmol) and sodium (23 mg, 1 mmol)] in MeOH at room temperature for 2 h gave the intermediate hydroxy acetal 81. This without purification was treated with 5 % aqueous H_2SO_4 (2 mL) and stirred for 30 min at room temperature. It was then diluted with water (5 mL), extracted with ether (3 x 10 mL) washed with satd. $NaHCO_3$ solution (5 mL), water (5 mL) and finally with brine (5 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave crude 82 which was purified by preparative thin layer chromatography. Yield 108 mg (43%).

IR spectrum ν_{max}(neat): 1650 (C=O), 1550 (NO_2) cm^{-1}.

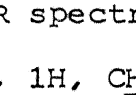
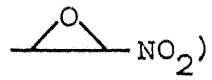
^1H NMR spectrum ($CDCl_3$): δ 1.9-2.25 (m, 2H, satd. CH_2), 2.4-2.9 (m, 4H, allylic CH_2 and $COCH_2$), 7.2 (s, 5H, aromatic).

Mass spectrum m/e (rel.int.): 220 (100, M^+-NO), 120 (56), 114 (38).

Anal. Calcd for $C_{12}H_{11}SNO_3$: C, 57.83; H, 4.42. Found: C, 57.79; H, 4.50.

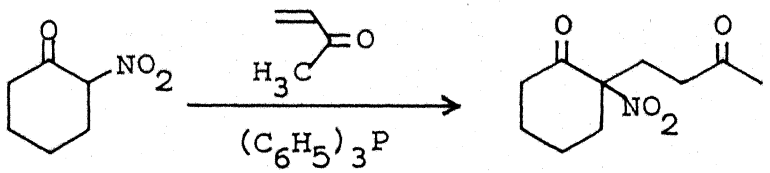
Note: The intermediate nitroepoxide 80 was isolated in 95% yield whose spectral data are given below.

IR spectrum ν_{max}(neat): 1550 (NO_2), 1350 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.16–1.56 (m, 4H, satd. CH_2), 1.58–2.24 (m, 1H, ), 2.46–2.88 (m, 1H,), 3.26 (s, 1H, ), 3.50–4.06 (m, 4H, acetal CH_2).

Mass spectrum, m/e (rel.int.): 184 (5, M^+-OH), 171 (17, M^+-NO), 155 (6, M^+-NO_2), 99 (100), 55 (100).

Preparation of 2-nitro-2(3-ketobutyl)cyclohexanone (84)



10 84

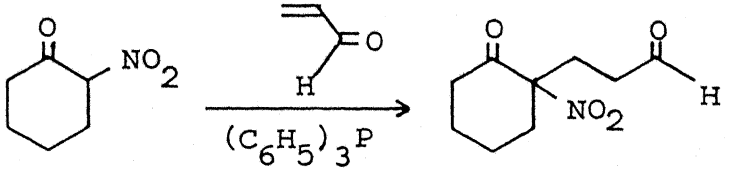
To a mixture of 2-nitrocyclohexanone, (10) (500 mg, 3.5 mmol) and methyl vinyl ketone (0.35 mL, 4.2 mmol) in THF (10 mL) was added triphenylphosphine (92 mg, 0.35 mmol) at room temperature under nitrogen atmosphere. The resultant mixture was stirred for 24 h after which CH_3I (0.5 mL) was added and stirred for an additional

15 min. After removing the solvent under reduced pressure, the residue was purified by column chromatography (benzene:ether 95:5) to obtain 84. Yield 675 mg (90%), b.p. 155–160°C/0.5 mm (lit.[46] b.p. 140–145°C/0.03 mm).

IR spectrum ν_{max}(neat): 1720 (br, C=O), 1545 (NO_2) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 2.1 (s, 3H, methyl), 1.5–3.1 (m, 12H, CH_2).

Preparation of 2-nitro-2(3-ketopropyl)cyclohexenone (83)



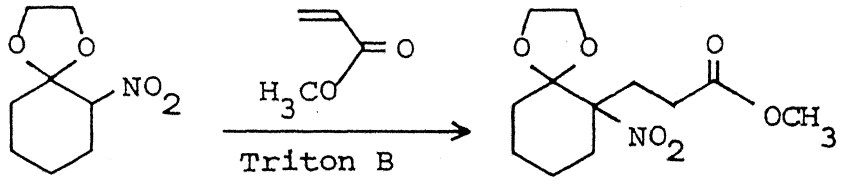
10 83

Following the above described procedure for 84, the reaction of 2-nitrocyclohexanone (10) (100 mg, 0.7 mmol), acrolein (47 mg, 0.84 mmol) and triphenylphosphine (10 mg) for 1 h at room temperature gave 83 which was purified by distillation. Yield 120 mg (86%), b.p. 157–160°C/0.2 mm (lit.[45] b.p. 160°C/0.02 mm).

IR spectrum ν_{max}(neat): 2730 (CHO), 1720 (br, C=O), 1540 (NO_2) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.5–3.0 (m, 12H, CH_2), 9.8 (s, 1H, CHO).

Preparation of 2-nitro-2(3-carbomethoxy propyl)cyclohexanone acetal (85)



67 85

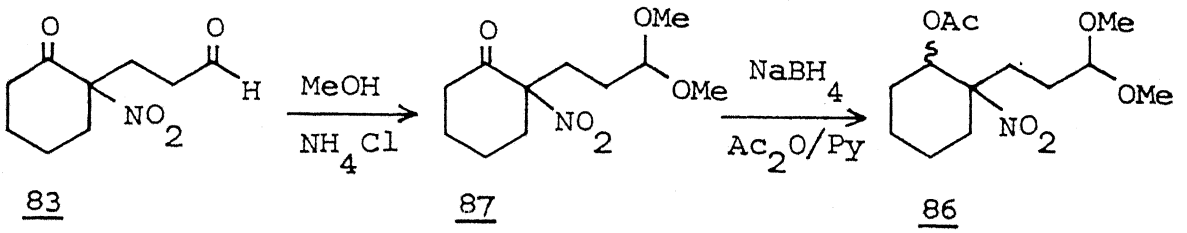
To a stirred mixture of 2-nitrocyclohexanone acetal (67) (1.0 g, 5.4 mmol) and methyl acrylate (0.6 mL, 6.6 mmol) in t-BuOH (15 mL) at room temperature under nitrogen atmosphere was added a drop of Triton B. After stirring for 5 h, the solvent was removed under reduced pressure, diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layer was washed with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude product which was purified by column chromatography by eluting with benzene to obtain 85 as a thick oil. Yield 1.3 g (88%).

IR spectrum ν_{max}(neat): 1730 (C=O), 1540 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.45-2.5 (m, 11H, CH_2), 2.7-3 (m, 1H, $\underline{CH}-\underline{C}-NO_2$), 3.7 (s, 3H, $OC\underline{H}_3$), 3.9 (s, 4H, acetal CH_2).

Mass spectrum, m/e (rel.int.): 273 (8, M^+), 227 (47, M^+-NO_2), 99 (100).

Preparation of 1-acetoxy-2(3,3-dimethoxy propyl)-2-nitrocyclo-xanone (86)



83 87 86

To 2-nitro-2(3-ketopropyl)cyclohexanone (83) (300 mg, 1.5 mmol) in dry methanol (5 mL) was added 5 mg of anhydrous ammonium chloride, the resultant mixture was allowed to stir at 50° for 15 min, then, at room temperature for 2 h. It was diluted with CH_2Cl_2 (25 mL), washed with satd.$NaHCO_3$ (5 mL) brine (5 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude product which was purified by distillation to obtain 87 as a colourless liquid. Yield, 250 mg (68%), b.p. 160-162°C/0.5 mm (lit.[47], b.p. 145°C/0.05 mm).

IR spectrum ν_{max}(neat): 1725 (C=O), 1545 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.2-2.35 (m, 9H, CH_2), 2.35-2.65 (m, 2H, $COCH_2$), 2.65-3.0 (m, 1H, $CH-\overset{|}{C}-NO_2$), 3.2 (s, 6H, OCH_3), 4.25 (t, J=6 Hz, 1H, $CH(OMe)_2$).

2-Nitro-2(3,3-dimethoxy propyl)cyclohexanone (87) (100 mg, 0.41 mmol) was reduced to the corresponding alcohol by $NaBH_4$ (16 mg, 0.42 mmol) in methanol at 0°C for 1 h. The crude alcohol was acetylated using acetic anhydride (0.08 mL, 0.82 mmol) and pyridine

(0.13 mL, 1.64 mmol) in CH_2Cl_2 at room temperature for 12 h. The product was purified by preparative thin layer chromatography by eluting with benzene:acetone (90:10) to obtain 86 as a thick oil. Yield 90 mg (80%).

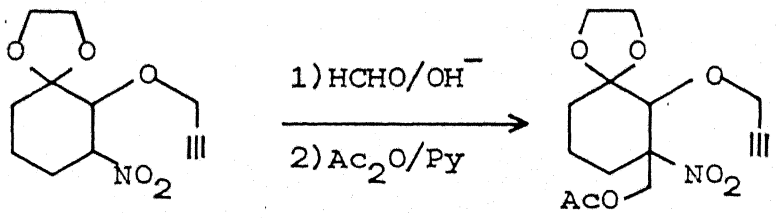
IR spectrum ν_{max}(neat): 1735 (C=O), 1540 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4 + $CDCl_3$): δ 1.2–2.9 (m, 12H, CH_2), 2.05–2.1 (2s, 3H, $COCH_3$), 3.3 (s, 6H, OCH_3), 4.02 and 4.28(2t, 1H, J=6 Hz, $CH(OMe)_2$), 5.37 and 5.55 (2m, 1H, $CH-OCOCH_3$).

Mass spectrum, m/e (rel.int.): 258 (73, M^+-OCH_3), 211 (15, M^+-OCH_3, $-NO_2$), 198 (42, M^+-OCH_3, $-CH_3COOH$), 75 (100).

Anal Calcd for $C_{13}H_{23}NO_6$: C, 53.98; H, 7.96. Found: C, 53.93; H, 7.92.

Preparation of 2-propargyloxy-3-acetoxymethyl-3-nitrocyclohexanone acetal (89)



79 89

A mixture of 79 (480 mg, 2 mmol) 37% HCHO (75 mg, 2.5 mmol) and NaOH (13 mg) in i-ProH (10 mL) was stirred at room temperature for 24 h. It was then diluted with CH_2Cl_2 (25 mL) and washed with brine (5 mL). Evaporation of the solvent gave a crude alcohol

which was acetylated without further purification. A mixture of alcohol, Ac_2O(0.38 mL,4 mmol) and pyridine (1 mL,) was stirred for 14 h at room temperature. It was diluted with water (10 mL), extracted with CH_2Cl_2 (3 x 15 mL), washed with water (10 mL), brine (5 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude product which was purified by column chromatography to obtain a thick liquid. Yield 460 mg (75%).

IR spectrum ν_{max}(neat): 3280 (C≡C-H), 2110 (C C), 1740 (C=O), 1540 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.4-2.75 (m, 6H, CH_2), 2.05 (s, 3H, $COC\underline{H}_3$), 3.8-4.25 (m, 6H, acetal CH_2 and CH_2OAc), 4.25-4.45 (m, 2H, $CH-O-C\underline{H}_2$), 4.45-4.65 (m, 1H, $C\underline{H}-O-CH_2$).

Mass spectrum m/e (rel.int.): 267 (10, M^+-NO_2), 195 (84, M^+-NO_2, $-CH_2OAc$), 151 (74), 99(100).

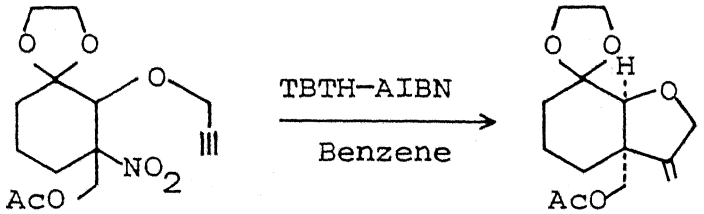
Anal. Calcd for $C_{14}H_{19}NO_7$: C, 53.67; H, 6.07. Found: C, 53.75; H, 6.00.

Preparation of tri-n-butyltin hydride (TBTH)

To a stirred solution of tri-n-butyltin chloride (1.0 g, 3.07 mmol) in ether (20 mL) at 0°C under nitrogen atmosphere was added $LiAlH_4$ (64 mg, 1.58 mmol). Stirring was continued at 0°C for 15 min and then at room temperature for 3 h. The reaction

mixture was slowly hydrolyzed with water (10 mL) with cooling and extracted with ether (3 x 15 mL). The organic layer was washed with ice-cold water (2 x 10 mL), brine (5 mL) and dried over anhydrous sodium sulphate. The crude product was distilled under reduced pressure. Yield 800 mg (90%), b.p. 75-80°C/0.5 mm (lit.[50], b.p. 68-74°C/0.3 mm).

Preparation of 90



89 90

A mixture of 89 (185 mg, 0.59 mmol) n-Bu_3SnH (224 mg, 0.77 mmol) and AIBN (29 mg, 0.17 mmol) in benzene (4 mL) was heated under nitrogen atmosphere for 5 h. After removal of the solvent, the residue was purified by column chromatography. [Eluent, Pet. ether:ether (80:20)] to obtain a thick liquid. Yield 80 mg (51%).

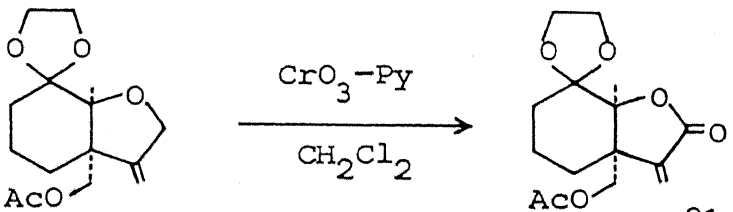
IR spectrum ν_{max}(neat): 1735 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.15-1.85 (m, 6H, satd. CH_2), 2.0 (s, 3H, OCH_3), 3.7 (s, 1H, $\underline{CH}$-O-CH_2), 3.8-4.1 (m, 6H, acetal CH_2 and $\underline{CH_2}$-OAc), 4.4 (s, 2H, CH-O-$\underline{CH_2}$), 4.8-4.95 (m, 2H, vinylic).

Mass spectrum m/e (rel.int.): 195 (36, M^+-CH_2-OAc), 99 (36), 83 (100).

Anal. Calcd for $C_{14}H_{20}O_5$: C, 62.68; H, 7.46. Found: C, 62.72; H, 7.50.

Preparation of 91



90 91

Chromium trioxide (450 mg, 4.5 mmol) was added to a mixture of pyridine (0.45 mL) and dichloromethane (5 mL) and the resultant mixture was stirred for 20 min at 20°C. To this mixture was added the substrate 90 (60 mg, 0.22 mmol) in CH_2Cl_2 (1 mL) and it was then refluxed for 1 h. After cooling to room temperature, satd. $NaHCO_3$ solution (20 mL) was added. It was extracted with CH_2Cl_2 (3 x 25 mL) and the combined extract was washed with water (10 mL), brine (5 mL), dried over anhydrous sodium sulphate and concentrated. The crude product was purified by preparative thin layer chromatography [silica gel, eluent, benzene:acetone 95:5)] to give a thick oil. Yield 40 mg (65%).

IR spectrum ν_{max}(neat): 1770 (C=O), 1740 (C=O) cm^{-1}.

^{1}H NMR spectrum ($CDCl_3$): δ 1.55–2.0 (m, 6H, satd. CH_2), 2.05 (s, 3H, $COCH_3$), 3.85–4.3 (m, 6H, acetal CH_2 and $\underline{CH}_2OAc$), 4.4 (s, 1H, $\underline{CH}$–O–C=O), 5.55 (s, 1H, olefinic), 6.4 (s, 1H, olefinic).

Mass spectrum m/e (rel.int.): 282 (16, M^+), 222 (20, M^+–CH_3COOH), 208 (90, M^+–CH_2OAc), 99 (100).

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.38. Found: C, 59.52, H, 6.43.

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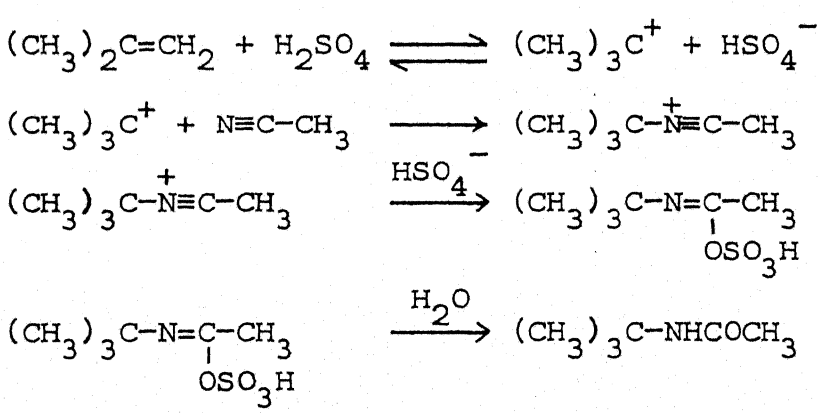
CHAPTER - II

RITTER REACTION ON CYCLOPROPYL KETONES AND CYCLOPROPYL CARBINOLS

II.1 Introduction

Ritter[1] in 1948 reported the formation of N-substituted amides from nitriles and olefins in the presence of concentrated sulphuric acid. Since then this reaction has been extended to a wide variety of compounds capable of generating carbocations and has emerged as an important synthetic reaction.[2]

The mechanism for the reaction between isobutene and acetonitrile is shown in Scheme II.1.

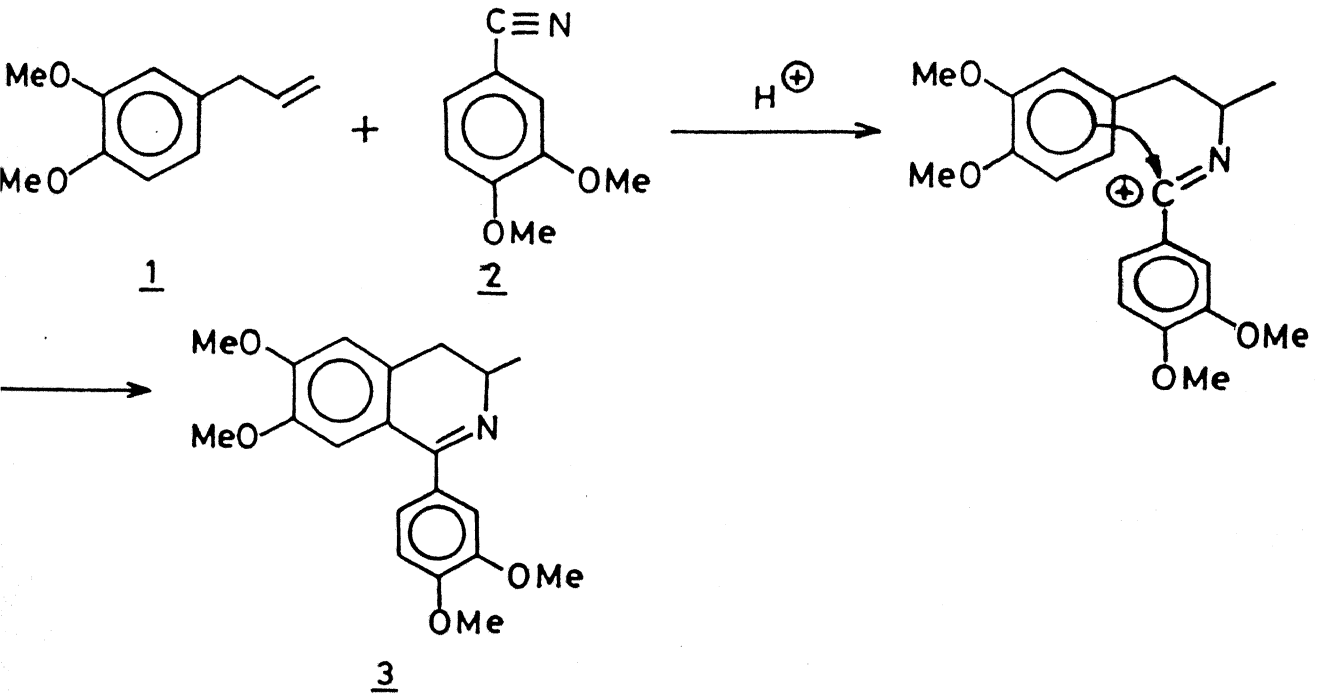


Scheme II.1

A variety of compounds, besides alkenes can serve as a source of carbocation.[2] These include alcohols,alkylhalides, aldehydes, esters, etc. These carbocations can be generated by using other acids (besides sulphuric acid) such as perchloric acid,[3] phosphoric acid[4], formic acid[5] and Lewis acids like boron trifluoride[6] etc.

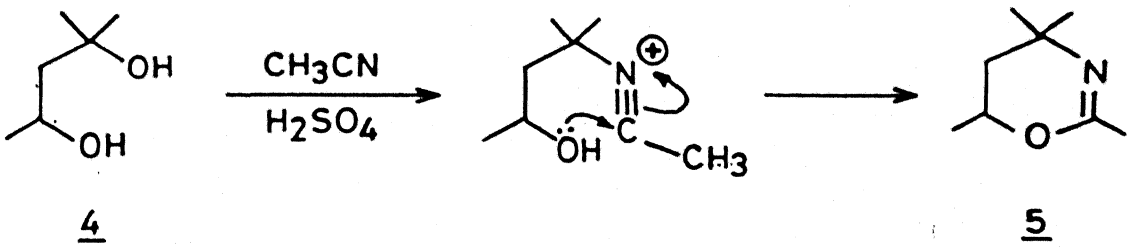
The Ritter reaction has been utilized in the synthesis of several interesting and useful heterocyclic compounds. For example, dihydroisoquinoline derivative 3 was synthesised from veratronitrile (2) and methyeugenol (1)[7] (Scheme II.2). Ritter and Tillmanns[8] have reported the synthesis of 1,3-oxazine 5 from 2-methyl-2,4-pentanediol (4) and acetonitrile (Scheme II.3).

The scope of Ritter reaction has been considerably extended by nitrile trapping by incipient carbocation generated from reactions which obviate the use of strong acids. Brown and Kurek[9] have shown that the incipient carbocation, generated from olefins in the presence of mercuric nitrate, add to nitriles and after treatment with sodium borohydride, give the same amide which would be obtained by classical Ritter reaction (Scheme II.4). This method provides a convenient alternative to the classical Ritter reaction. This reaction has recently been used in the synthesis of the key intermediate 6, for the total synthesis of the alkaloid hobartine (7) starting from α-pinene[10] (Scheme II.5). Recently allyl amides were synthesised from olefins with phenylselenyl chloride and nitriles (Scheme II.6).



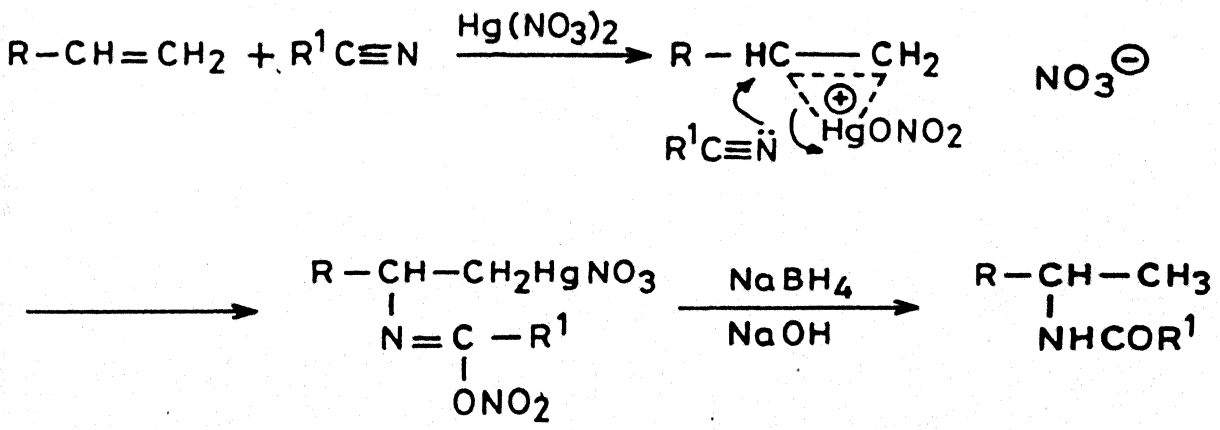
1 2 3

Scheme II.2

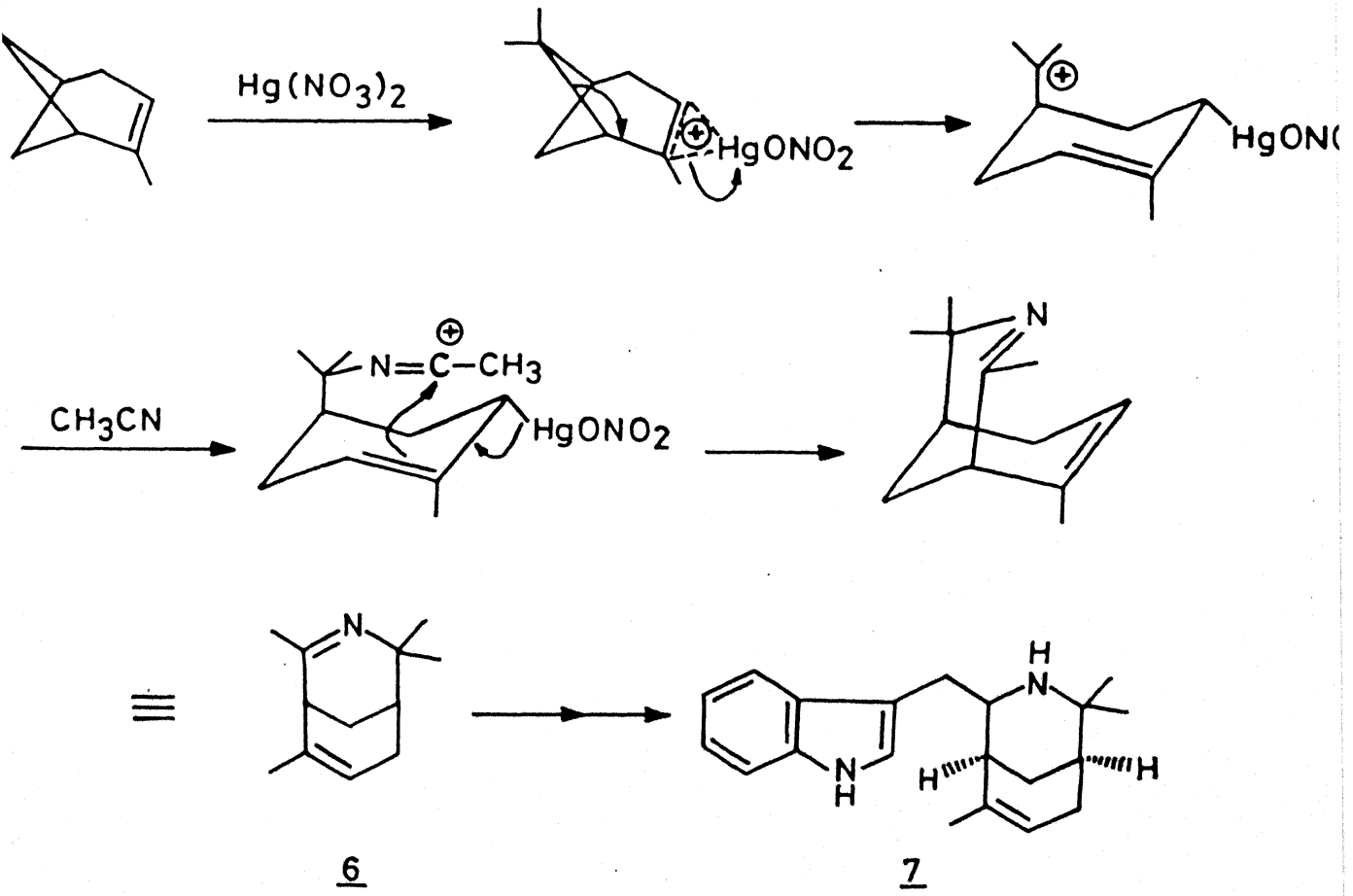


4 5

Scheme II.3

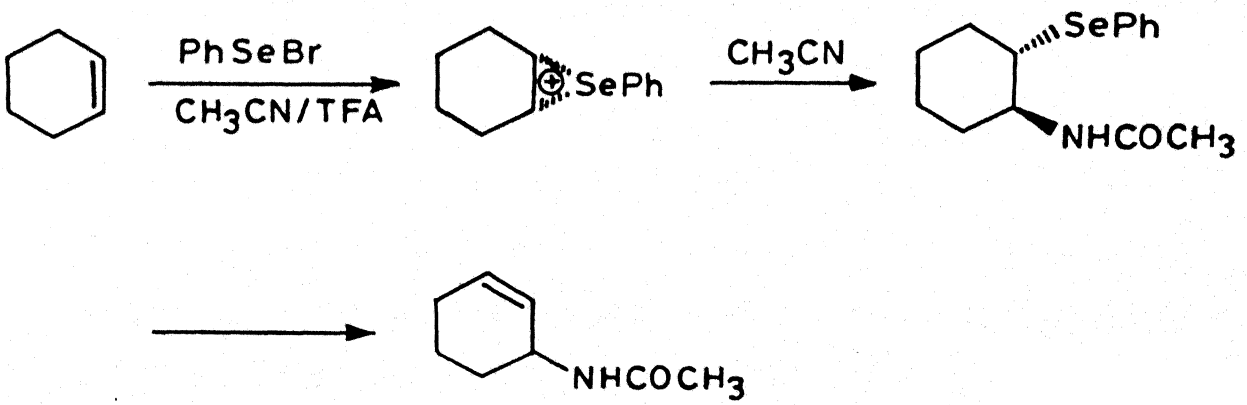


Scheme II.4



6 7

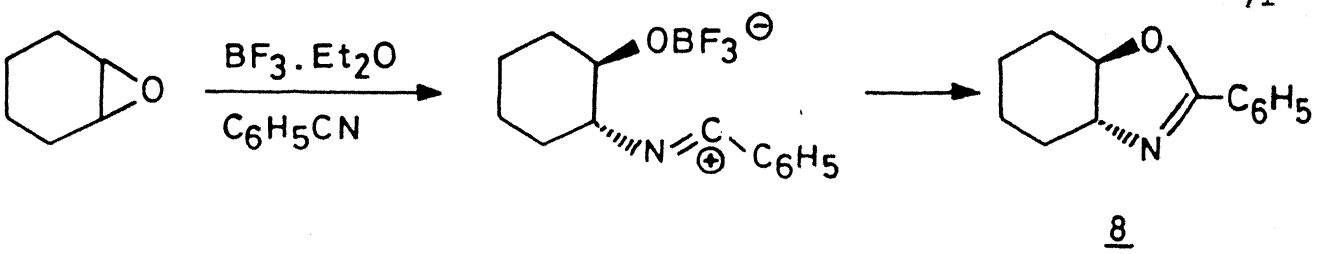
Scheme II.5



Scheme II.6

Lewis acids have also been successfully used to generate incipient carbocations for Ritter reaction. Norman et al.[11] have stereospecifically synthesized dihydro-1,3-oxazolones 8 by nitrile attack on incipient carbocations generated from oxiranes by the action of boron trifluride (Scheme II.7). Although primary alcohols do not react under normal Ritter reaction conditions,[12] primary halides react with nitrilium salts derived from a Lewis acid and a nitrile. For example, the reaction of 9 with acetonitrile-$SnCl_4$ complex gave 10.[13] Thakur and Vankar[14] have recently extended this reaction to chloromethylphenylsulphides to obtain pharmacologically active 2H-benzothiazines 12 (Scheme II.8). Rao and Vankar[15] from our laboratory, reported for the first time, the Ritter reaction on Pummerer intermediate.Thus, the reaction of sulphoxides 13 with nitriles in the presence of trifluoroacetic anhydride (TFAA) and trifluoroacetic acid gave N-substituted amides 14 (Scheme II.9).

As mentioned earlier (vide supra), a variety of compounds, besides alkenes, can serve as a source of carbocation for the Ritter reaction. Surprisingly there is no report in the literature where cyclopropyl carbinols and cyclopropyl ketones, as a source of carbocation for the Ritter reaction. Considering the interesting chemistry of cyclopropyl carbinols and cyclopropyl ketones (vide infra) the present study was undertaken to find out the behaviour of nitriles towards cyclopropylcarbinyl cations



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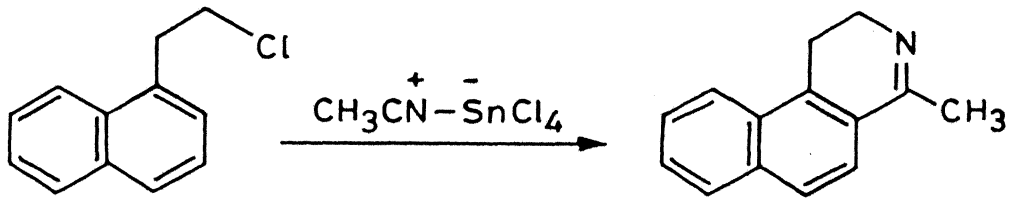
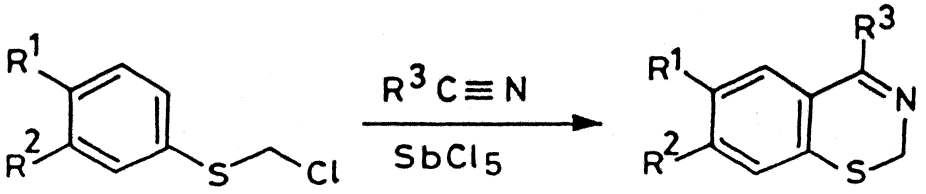
Scheme II.7

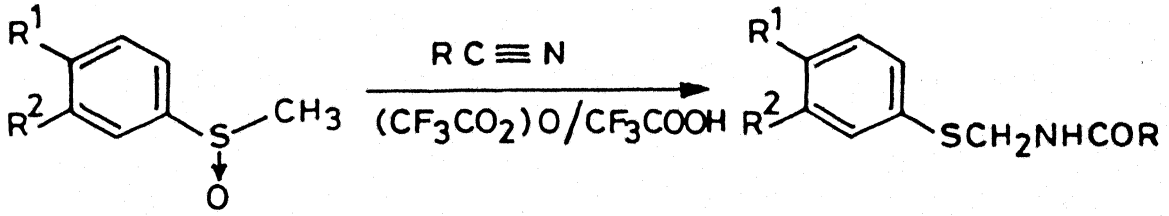


9 10



11 12

Scheme II.8

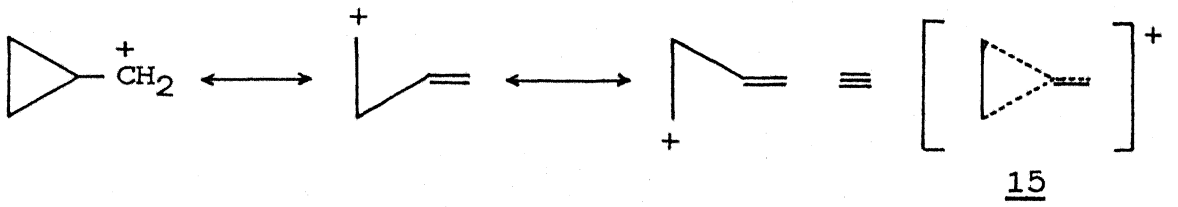


13 14

Scheme II.9

derived from cyclopropyl carbinols and cyclopropyl ketones in the presence of concentrated sulphuric acid i.e., typically, under Ritter reaction conditions.

When a cation is generated α to the cyclopropyl ring, the system relieves its strain by conjugation of the bent orbitals of the cyclopropyl ring with the vacant p-orbital of the carbocation, resulting in the opening of the three membered ring and formation of a homoallyl cation 15.[16] This cyclopropylmethyl-homoallyl

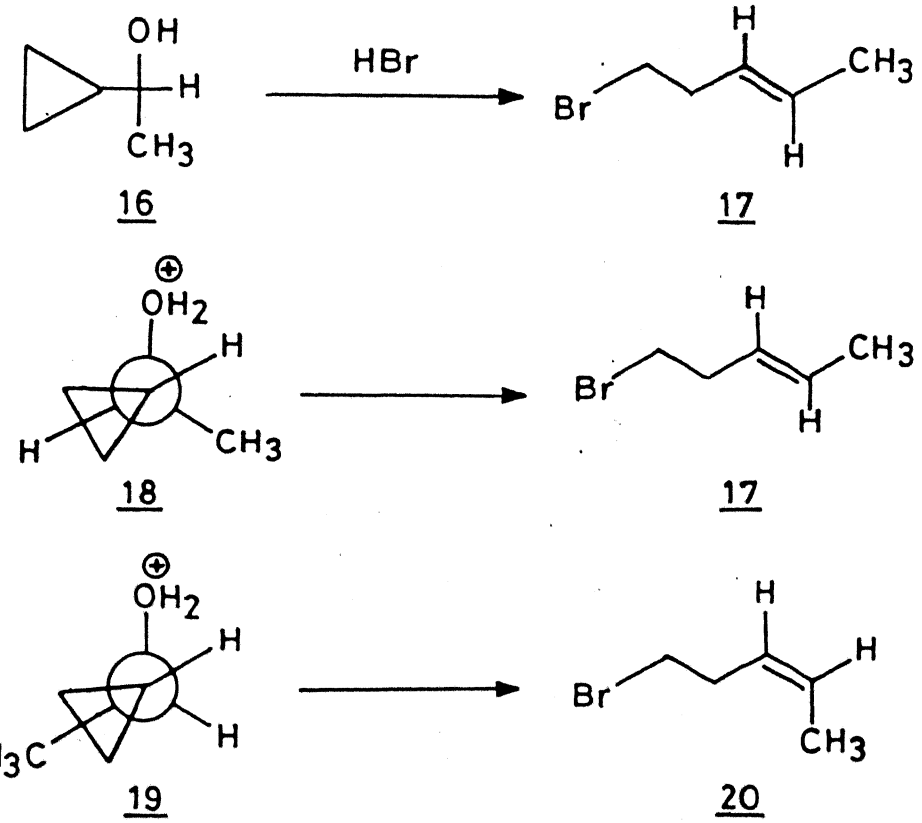


15

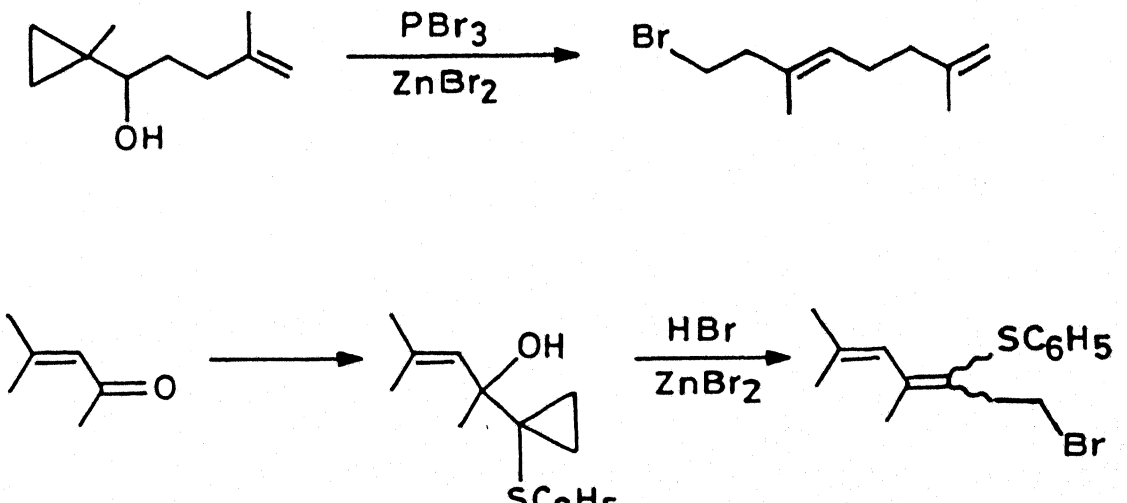
Scheme II.10

rearrangement (Scheme II.10) plays a major role in synthetic utilization of the cyclopropyl ring function.[17]

Julia et al.[18] were the first to exploit the synthetic utility of cyclopropylcarbinyl-homoallyl rearrangement. The reaction of cyclopropyl carbinol 16 with HBr gave trans-homoallyl bromide 17 with 90-95% stereoselectivity. Highly stereoselective formation of the trans olefin can be visualized from the Newman projection of the transition states. Transition state 18 which leads to the trans olefin 17 is favoured over the transition state 19 (Scheme II.11). The reaction of cyclopropyl carbinols with



Scheme II.11



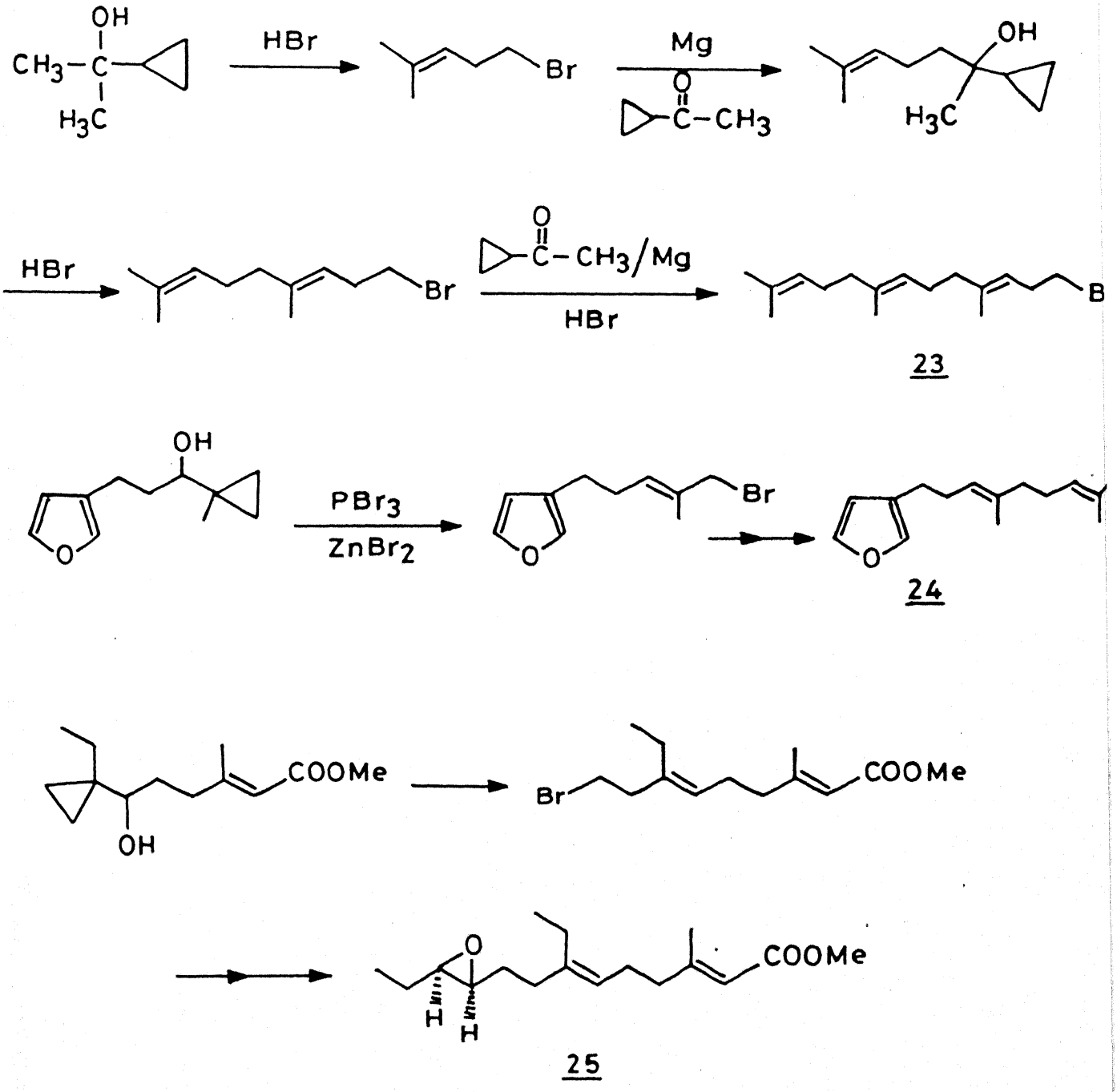
Scheme II.12

PBr_3-$ZnBr_2$ also gave trans-homoallyl bromides with high degree of stereoselectivity.[19] Recently Miller et al.[20] have reported the acid catalyzed rearrangement of 21 to functionalised conjugate diene 22 (Scheme II.12).

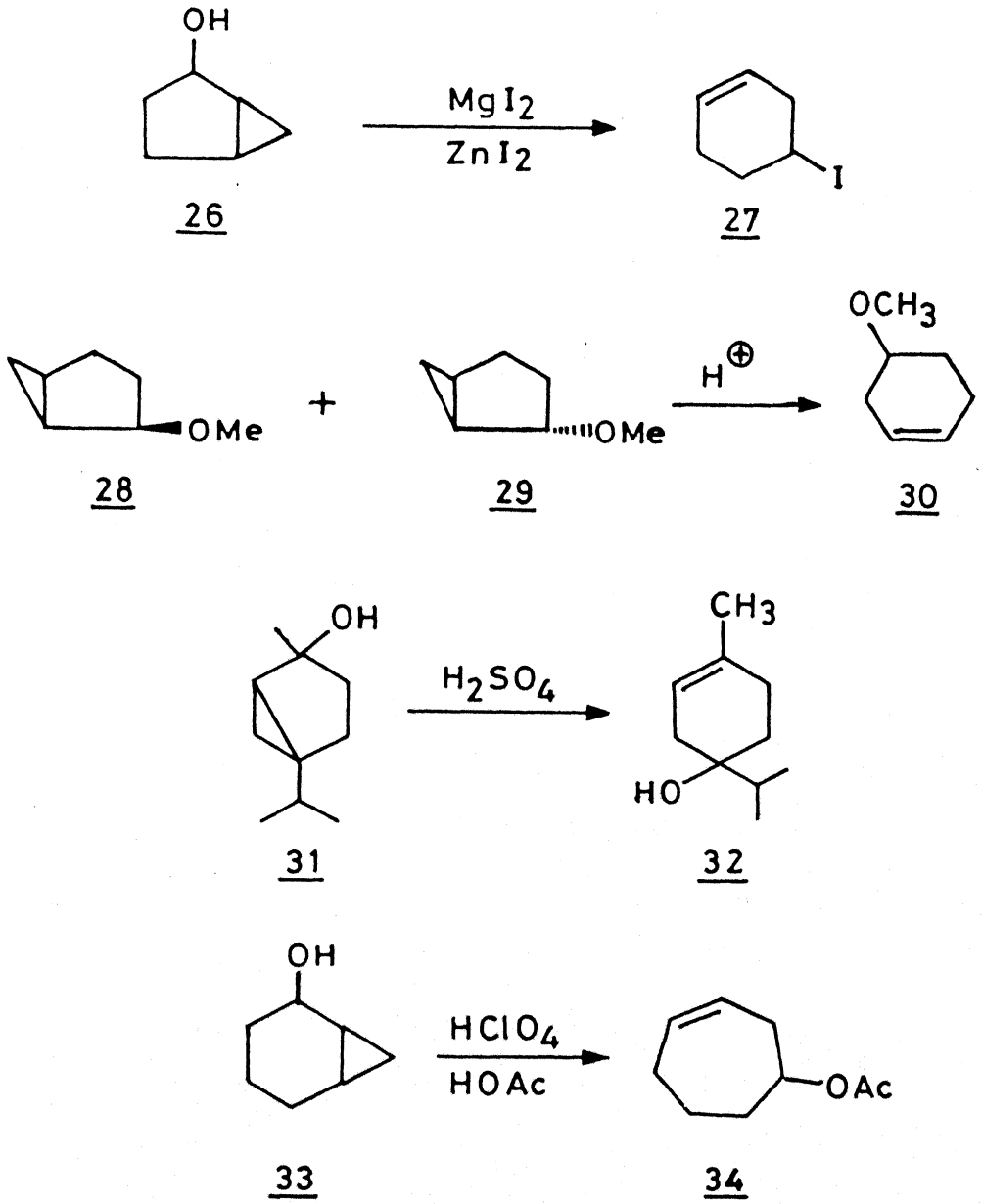
Potential synthetic applications of the cyclopropylcarbinyl-homoallyl rearrangement are shown in Scheme II.13. The cyclopropyl-carbinyl-homoallyl rearrangement has been utilized in the synthesis of long chain isoprenoids 23.[18] This rearrangement has also been utilized as a key step in the synthesis of a natural product Dendrolasin 24[21] and also for the synthesis of the Cecropia juvenile hormone 25.[22]

Cyclopropylcarbinyl-homoallyl rearrangement has also been observed in bicyclic system where the ring expanded homoallyl products were found to form as major products. For example, bicyclo (3.1.0)hexan-2-ol (26) with magnesium iodide and zinc iodide gave 4-iodocyclohexene (27) as a major product.[23] A mixture of 28 and 29 on prolonged reaction with sulphuric acid gave a thermodynamically more stable product 30.[24] Similarly the reaction of 31 gave 32[25] (Scheme II.14). Friedrich et al.[26] have reported the formation of the ring expanded homoallyl acetate 34 on acetalysis of 33 (Scheme II.14).

Cyclopropylcarbinyl cation can be generated from cyclopropyl ketones in the presence of an acid. Thus, cyclopropyl ketones on treatment with an acid (protic or Lewis) or any other strongly


OH
CH3–C
H3C
HBr
Br
Mg
O
C–CH3
OH
H3C
HBr
Br
O
C–CH3/Mg
HBr
B
23
OH
O
PBr3
ZnBr2
Br
O
24
COOMe
OH
Br
COOMe
O
H
H
COOMe
25

Scheme II.13



26 27 28 29 30

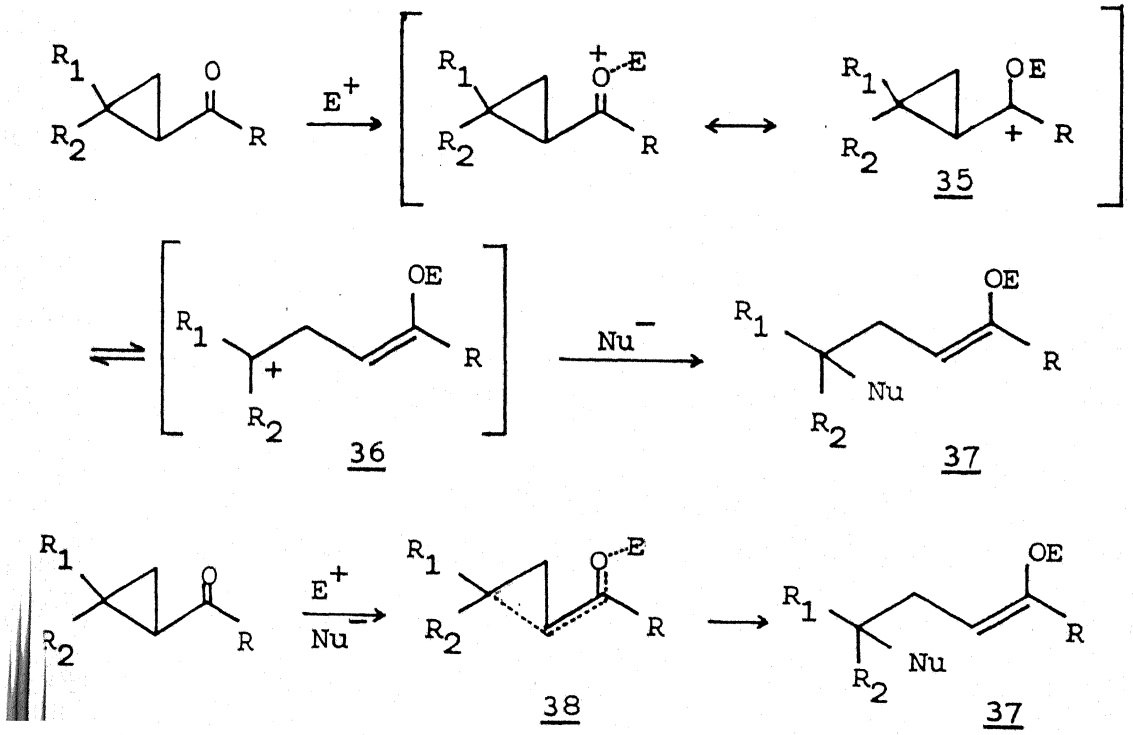
31 32

33 34

Scheme II.14

electrophilic reagent, the carbonyl group gets activated to generat a cyclopropylcarbinyl cation 35 which on conjugation with the cyclo propyl ring leads to the homoallylic type cation 36 (as in the case of cyclopropyl carbinols). This incipient carbocation can be irreversibly trapped by a nucleophile present in the reaction medium. It is proposed that the whole process may take place in a concerted way[27] as shown by the transition state 38 (Scheme II.15

Various nucleophiles have been utilized in the literature to open the electrophilically activated cyclopropyl ketones and this methodology has been applied in the synthesis of various natural products.

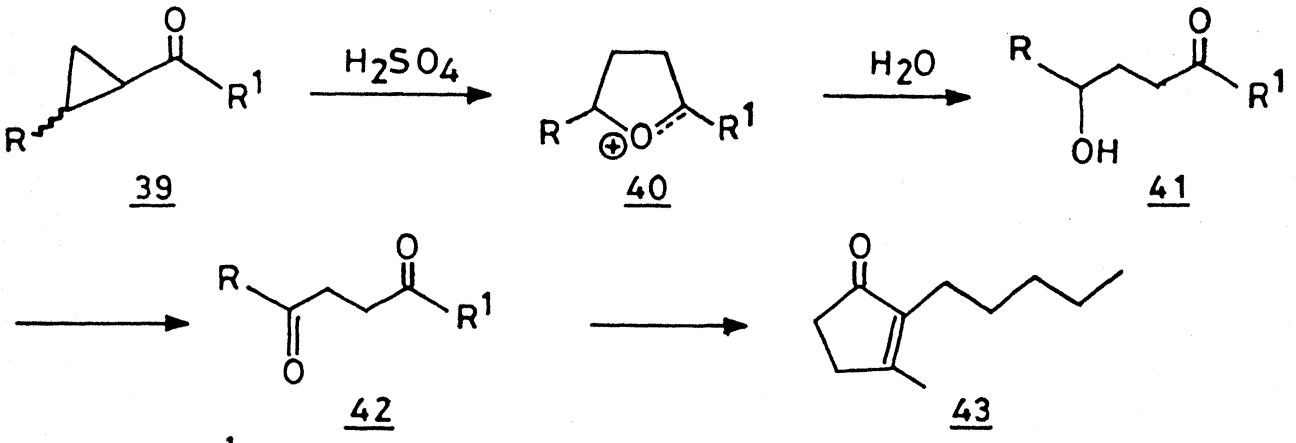


Scheme II.15

Nakai et al.[28] have utilized 1,2-dicarbonyl compound 42 generated from the cyclopropyl ketone 29 for the synthesis of the natural product dihydrojasmone (43) (Scheme II.16). Stork et al.[29] have carried out interesting and imaginative cyclizations by Lewis acid catalyzed opening of cyclopropyl ketones. Thus, a suitably located olefin can undergo π-cation cyclization with the incipient cation generated at the ν-position by opening of the cyclopropyl ketone system. The endo-bicyclo (3.1.0)hexanone 44 underwent a series of cyclization with $SnCl_4$ to give 45 (Scheme II.17). This methodology was applied by Corey[30] in the stero-selective synthesis of the sesquiterpene Cedrene (48) (Scheme II.1

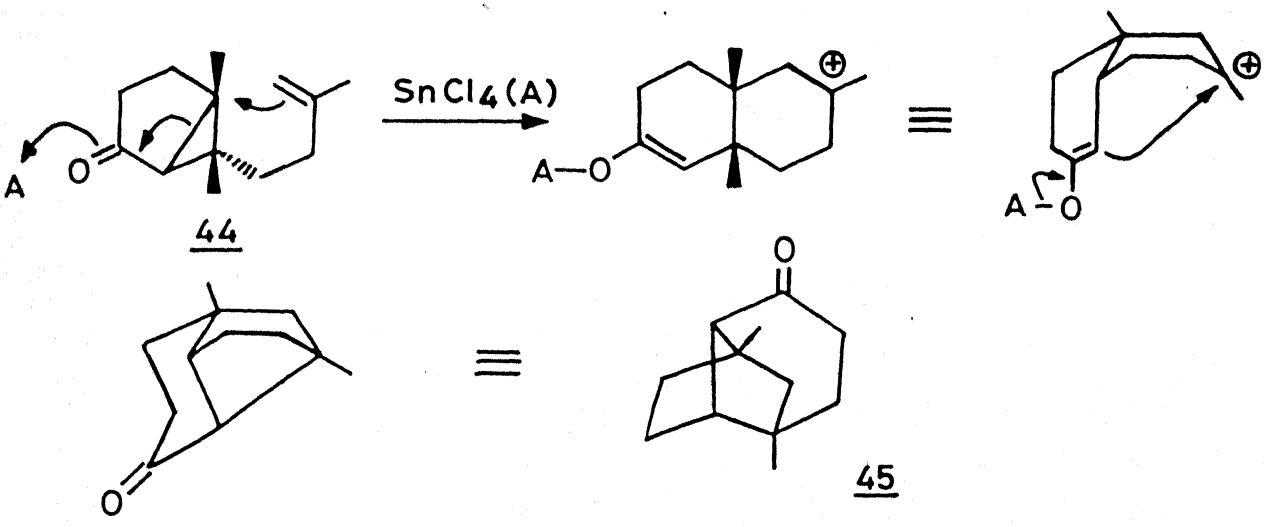
Several electrophilic reagent-nucleophile combinations have been utilized to open the cyclopropyl ketone systems. In the absence of an added nucleophile, the counter anion of electro-philic reagents opens the cyclopropane ring. Various reagents such as, acetyl methanesulphonate (AcOMs)-I^-,[27] pyridinium hydro-chloride,[31] iodotrimethylsilane,[32] lithium phenylselenolate,[33] $CF_3COOSiMe_3$,[34] HOAc-HBr,[35] have been reported in the literature to open cyclopropyl ketones.

Thus, generation of cyclopropylcarbinyl cation from a carbinol, opening of the cyclopropane ring, followed byan attack of a suitable nucleophile provides a general method for the pre-paration of homoallylic compounds with high degree of stereo-selectivity. Similarly cyclopropyl ketones could also be opened by means of an acid followed by nucleophilic attack to lead to a variety of molecular frameworks.

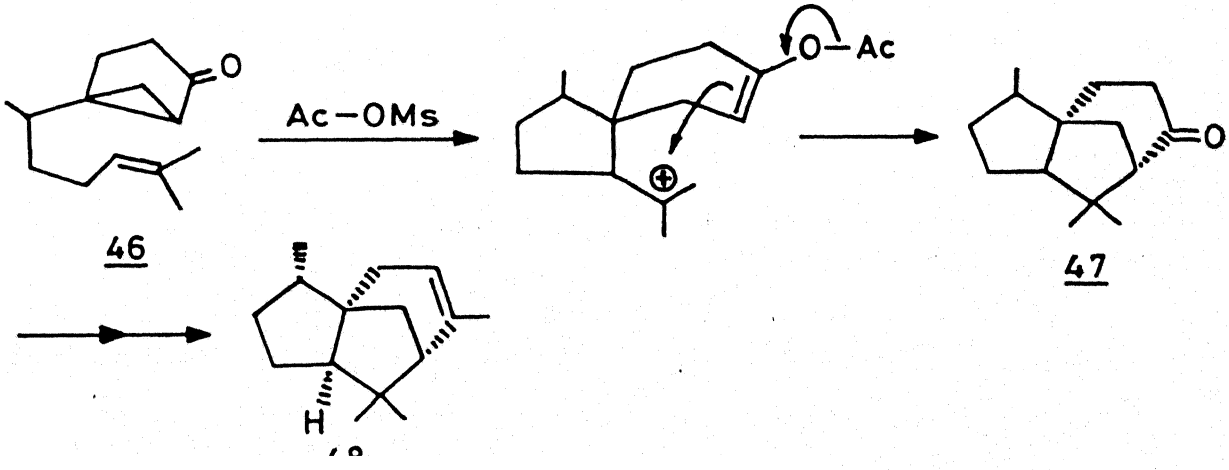


R = CH_3, R^1 = C_6H_{13}

Scheme II.16



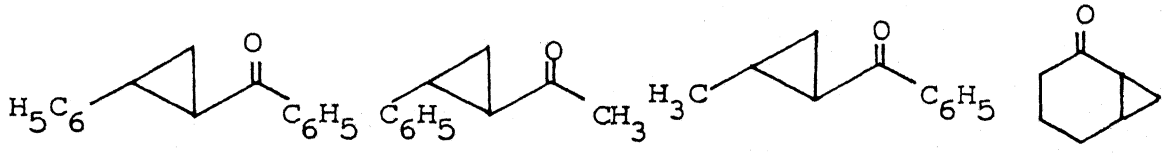
Scheme II.17



II.2 Results and Discussion

In the introduction part of this chapter it has been described from the literature data that both cyclopropyl carbinols and cyclopropyl ketones undergo ring opening reactions with nucleophiles in the presence of an acid. The present study was undertaken to find out the behaviour of nitriles towards cyclopropylcarbinyl cations generated from cyclopropyl carbinols and cyclopropyl ketones under Ritter reaction conditions.

Initial studies were carried out with cyclopropyl ketones. Various substrates chosen for the present study are shown below.

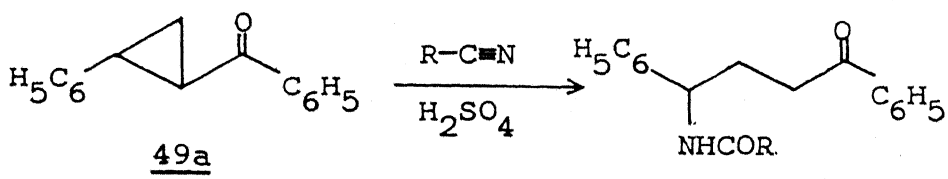


49a 49b 49c 50

These substrates viz. trans-1-benzoyl-2-phenylcyclopropane (49a), trans-1-acetyl-2-phenylcyclopropane (49b) and trans-1-benzoyl-2-methylcyclopropane (49c) were prepared by cyclopropanating the corresponding enones as per the literature procedure[36,37] using trimethylsulphoxonium iodide. Bicyclo(4.1.0)heptan-2-one (50), on the other hand was prepared by CrO_3 oxidation of the corresponding cyclopropyl carbinol 58b which in turn was prepared by following the literature procedure,[38] by cyclopropanation of

cyclohexenol. Structures of these substrates were confirmed based on their spectral data (cf. experimental section) and comparison with literature data.

The reaction of acetonitrile with 49a in the presence of conc. H_2SO_4 at 0°C for 6 h was found to give the amide 51a in 64% yield. This amide showed absorptions at 3260 (ν_{NH}), 1675 ($\nu_{C=O}$),



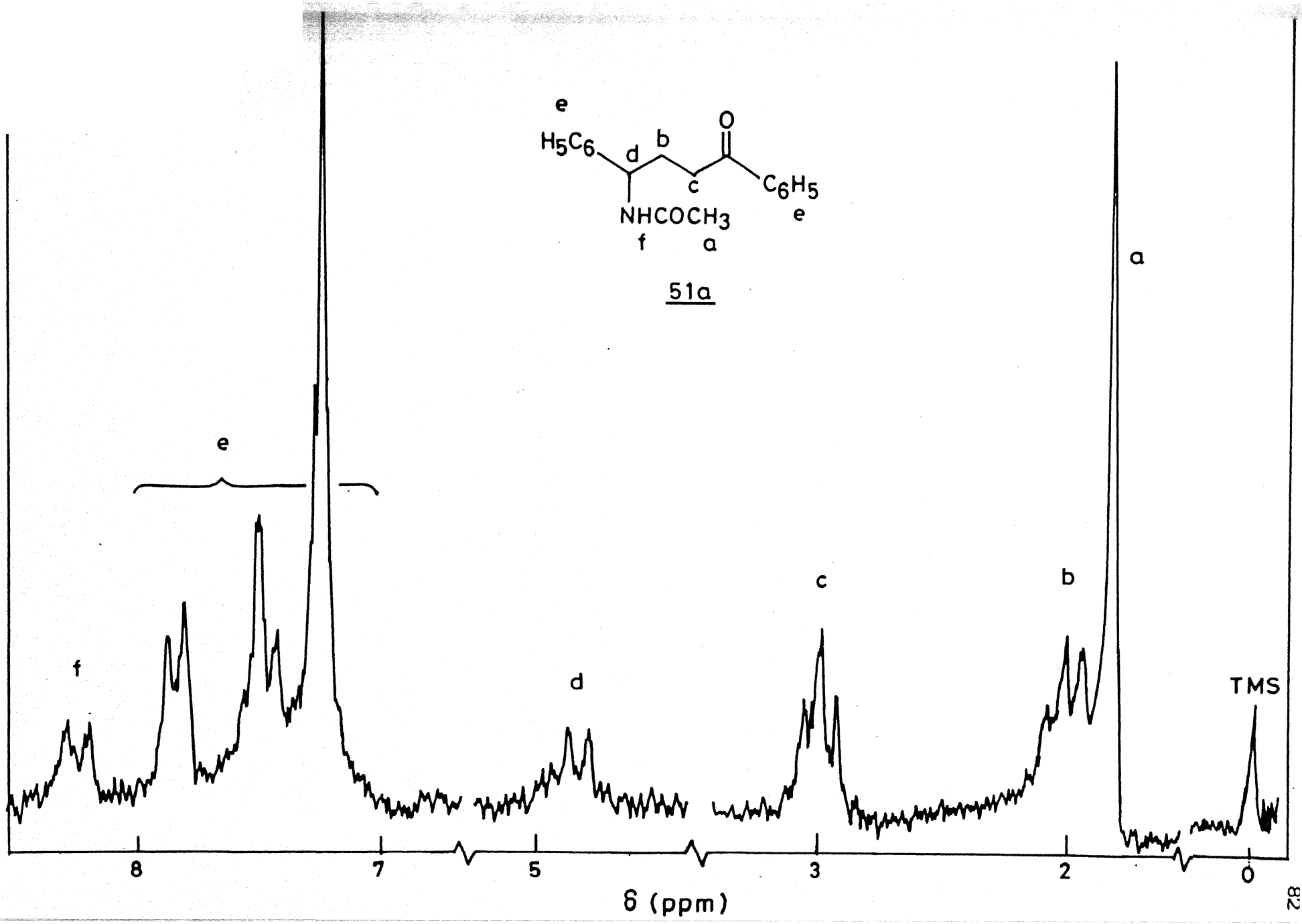
49a

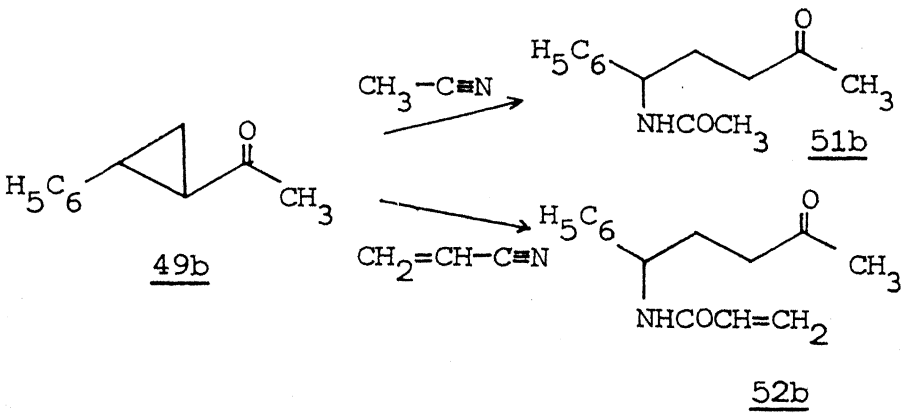
51a, R = CH_3

52a R = $CH{=}CH_2$

and 1640 (ν_{C-NH}^{O}) cm^{-1} in its IR spectrum. Its ^1H NMR spectrum (Fig.II.1) showed absorptions at δ 1.84 (s, 3H, $COCH_3$), 1.88–2.2 (m, 2H, CH_2), 3.02 (t, 2H, J=6 Hz, $COCH_2$), 4.68–4.92 (m, 1H, CH–NH), 7.08–7.98 (m, 10H, aromatic), 8.2 (br, 1H, NH) and mass spectrum showed M^+ peak at 281. These data confirm the structure assigned to the amide 51a. Under similar conditions when acrylonitrile was used, the corresponding amide 52a was obtained in 55% yield. The structure was assigned on the basis of spectral and analytical data (cf. experimental section).

In a similar fashion, the reaction of 49b with acetonitrile at 0°C for 6 h gave the amide 51b and with acrylonitrile for 6 h gave the amide 52b in 55% and 45% yields respectively (Scheme II.19). The amide 51b showed absorptions at 3340 (ν_{NH}), 1710 ($\nu_{C=O}$),

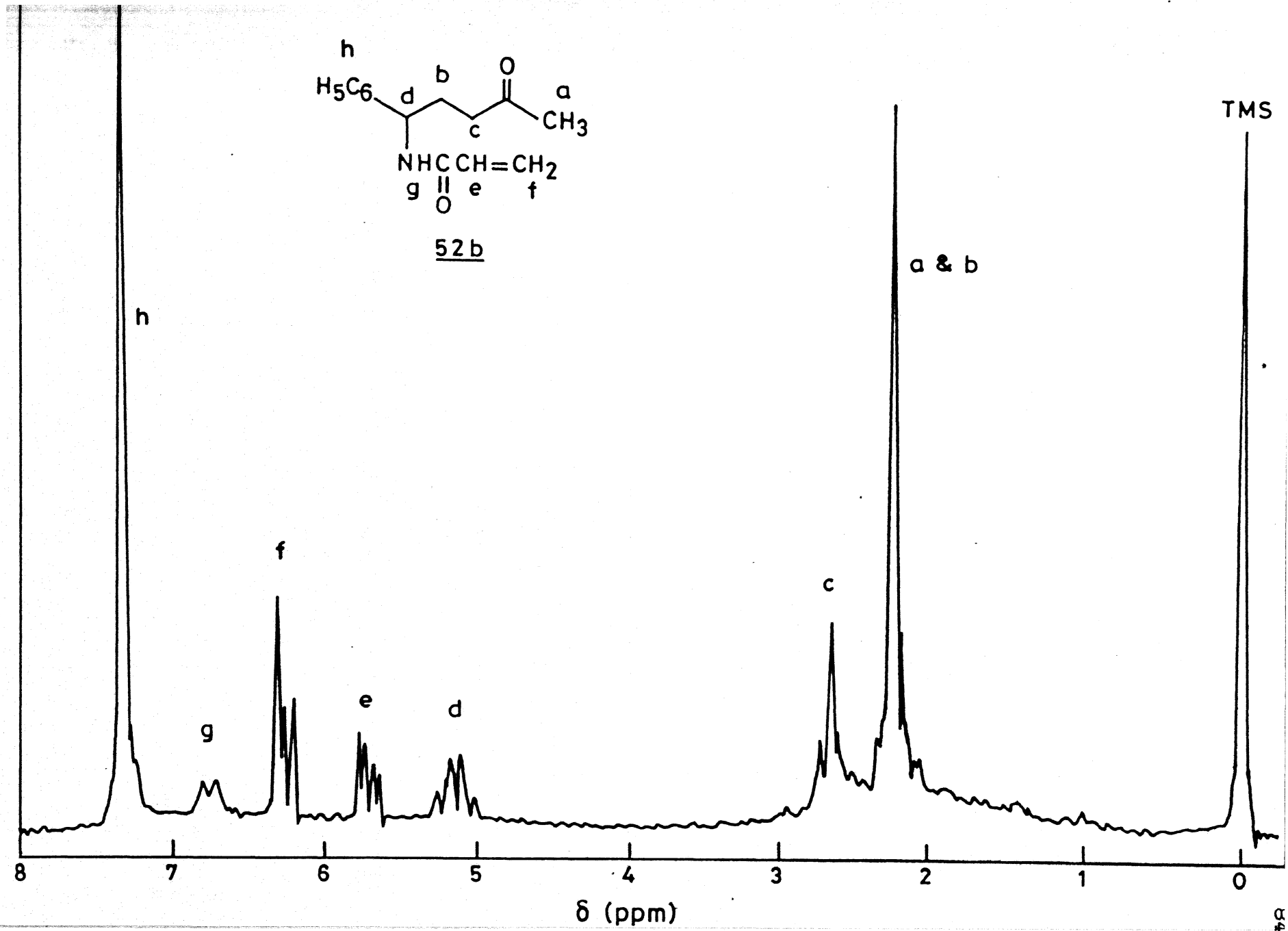

e
H5C6
d
b
c
O
C6H5
NHCOCH3
f
a
e
51a
e
f
d
c
b
a
TMS
8
7
5
3
2
0
δ (ppm)



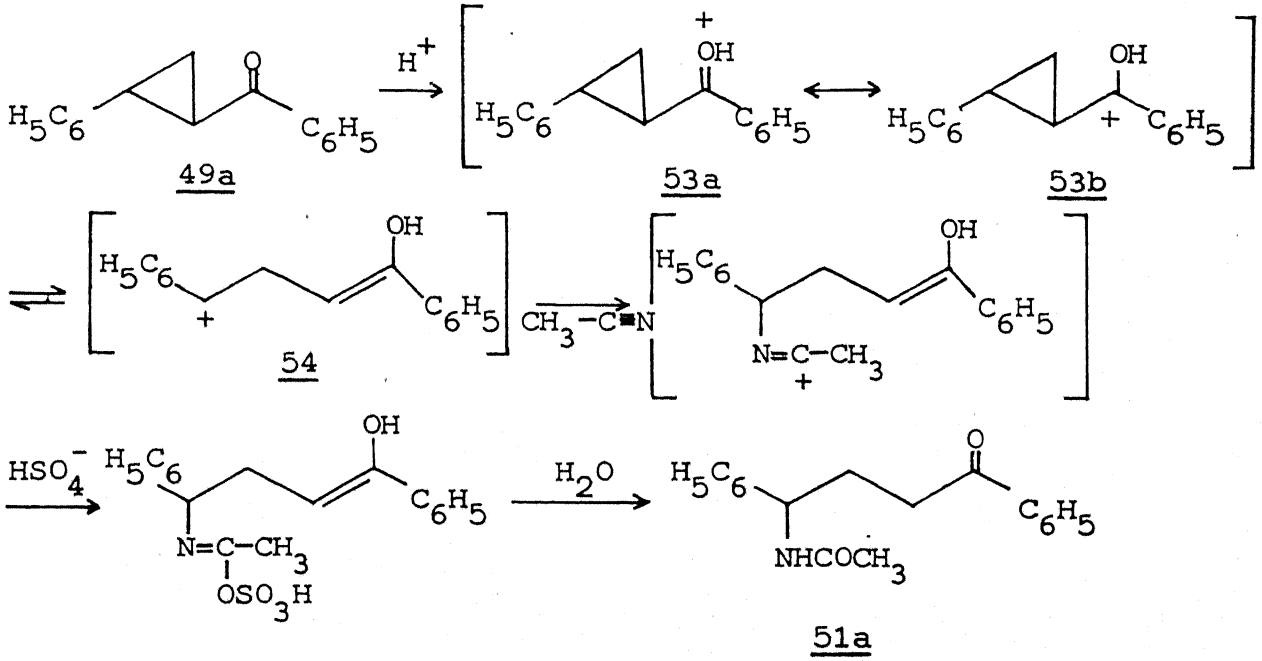
Scheme II.19

1660 (ν_{C-NH}^{O}) cm^{-1} in its IR spectrum. Its ^1H NMR spectrum showed absorptions at δ 1.95 (s, 3H, $NHCOCH_3$), 2.15 (s, 3H, $COCH_3$), 1.9–2.2 (m, 2H, CH_2), 2.6 (t, 2H, J=6 Hz, $COCH_2$), 4.8–5.2 (m, 1H, CH–NH), 6.45–6.9 (br, 1H, NH), 7.18 (m, 5H, aromatic). Mass spectrum showed a molecular ion peak at 219. These data confirm the structure assigned to 51b.

The structure of 52b was assigned on the basis of its spectral and analytical data. Thus, its IR spectrum showed absorptions at 3320 (ν_{NH}), 1710 ($\nu_{C=O}$), 1660 (ν_{C-NH}^{O}), 1625 ($\nu_{C=C}$), 1605 ($\nu_{C=C}$) cm^{-1}. Its ^1H NMR spectrum (Fig. II.2) showed absorptions at δ 2.2 (s, 3H, $COCH_3$), 2.0–2.35 (m, 2H, CH_2), 2.6 (t, 2H, J=6 Hz, $COCH_2$), 5.0–5.3 (m, 1H, CH–NH), 5.65 (dd, 1H, J=9 Hz, 4.5 Hz vinylic), 6.2 (m, 2H, vinylic), 6.55–6.85 (br, 1H, NH), 7.35 (m, 5H, aromatic) and the mass spectrum showed M^+ peak at 231.

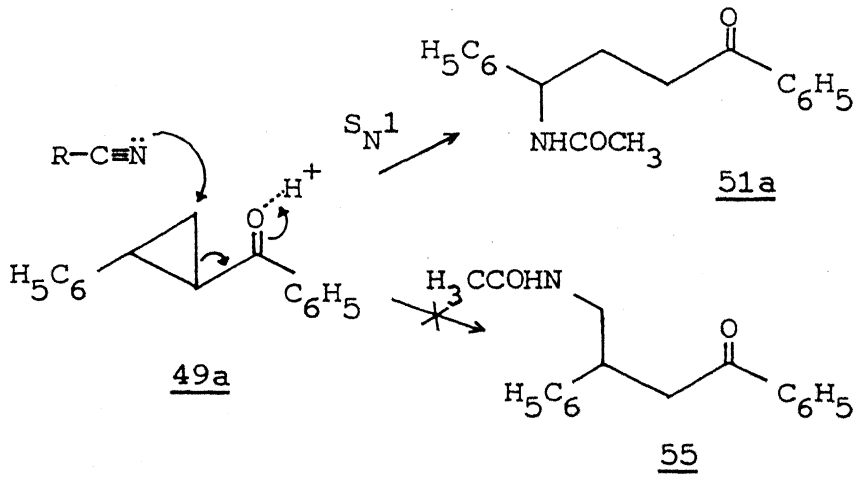

h
H5C6
d
b
O
a
CH3
c
NHC CH=CH2
g e f
O
52b
TMS
a & b
h
f
c
g
e
d
8
7
6
5
4
3
2
1
0
δ (ppm)

A plausible mechanism for the formation of the amides, for example 51a from the cyclopropyl ketone 49a and acetonitrile in the presence of conc. H_2SO_4, is shown in Scheme II.20. Initial protonation on carbonyl oxygen of the cyclopropyl ketone 49a led



Scheme II.20

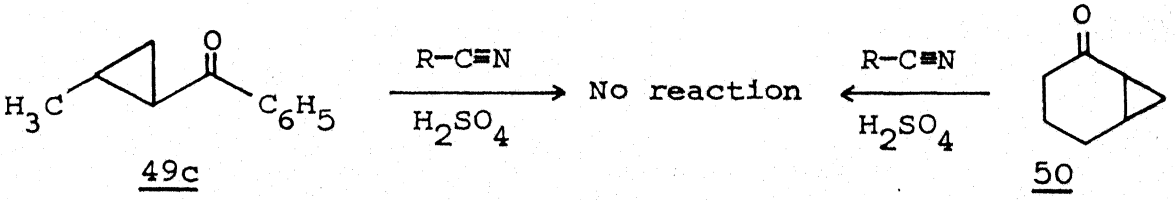
to the formation of cyclopropylcarbinyl cation 53b which on ring opening gave a homoallyl type cation 54. This cation 54 was irreversibly trapped by the nitrile present in the reaction medium to give the amide 51a. Formation of only one product i.e. 51a indicated that the reaction proceeded following an S_N1 type mechanism. Had the reaction proceeded involving the nitrile attack at the methylene carbon (less hindered side), one would have expected to obtain amide 55 rather than 51a (Scheme II.21). Formation



Scheme II.21

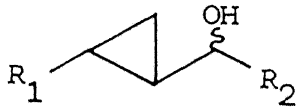
of the amide 51a and hence the reaction proceeding according to S_N1 mechanism is not unexpected because the nitrile is not a good nucleophile to open the cyclopropane ring from the less hindered side in a S_N2 manner. Further, the stability of the carbocation formed after the ring opening plays a major role in the product formation.

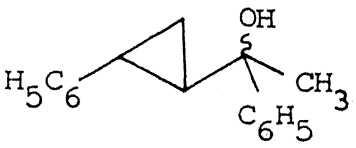
Reactions of cyclopropyl ketones 49c and 50 with both acetonitrile and acrylonitrile did not give any amide even after prolonged treatment at room temperature (48 h). On the other hand, refluxing the reaction mixture gave a complex mixture from which any product isolation became difficult.



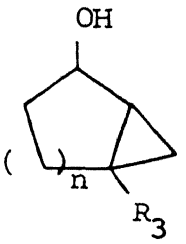
Behaviour of nitriles towards these cyclopropyl ketones can be explained again on the basis of the mechanism proposed earlier (Scheme II.19). The inertness of these substrates to undergo ring opening could be attributed to the fact that the protonated carbonyl group does not allow the cyclopropyl ring to open unless either the carbocation to be formed is stable or the attacking nucleophile is a strong one. Furthermore, the protonated carbonyl is not equivalent to a good leaving group, which if it were, would have forced the cyclopropane ring to open. Unless one of these factors is taken care, the success of the reaction is not met with. While our study was in progress,[39a] Wenkert et al.[39b] have published a brief note of the formation of amides from cyclopropyl ketones and cyclopropyl carbinols with $Me_3Si^+ClO_4^-$ in the presence of nitriles.

The formation of cyclopropylcarbinyl cation, followed by ring opening will not be difficult in the case of cyclopropyl carbinols because protonated alcoholic group is a good leaving group. In order to test this, various cyclopropyl carbinols 56a-c, 57 and 58a-e (Chart II.1) were reacted with two nitriles viz., acetonitrile and acrylonitrile in the presence of conc.H_2SO_4. Alcohols 56a-c were prepared by sodium borohydride reduction of the corresponding ketones 49a-c whereas alcohol 57 was prepared in 83% yield by the addition of PhMgBr to cyclopropyl ketone 49b.





57



56a $R_1 = R_2 = C_6H_5$

b $R_1 = C_6H_5$, $R_2 = CH_3$

c $R_1 = CH_3$, $R_2 = C_6H_5$

58a n = 1, R_3 = H

b n = 2, R_3 = H

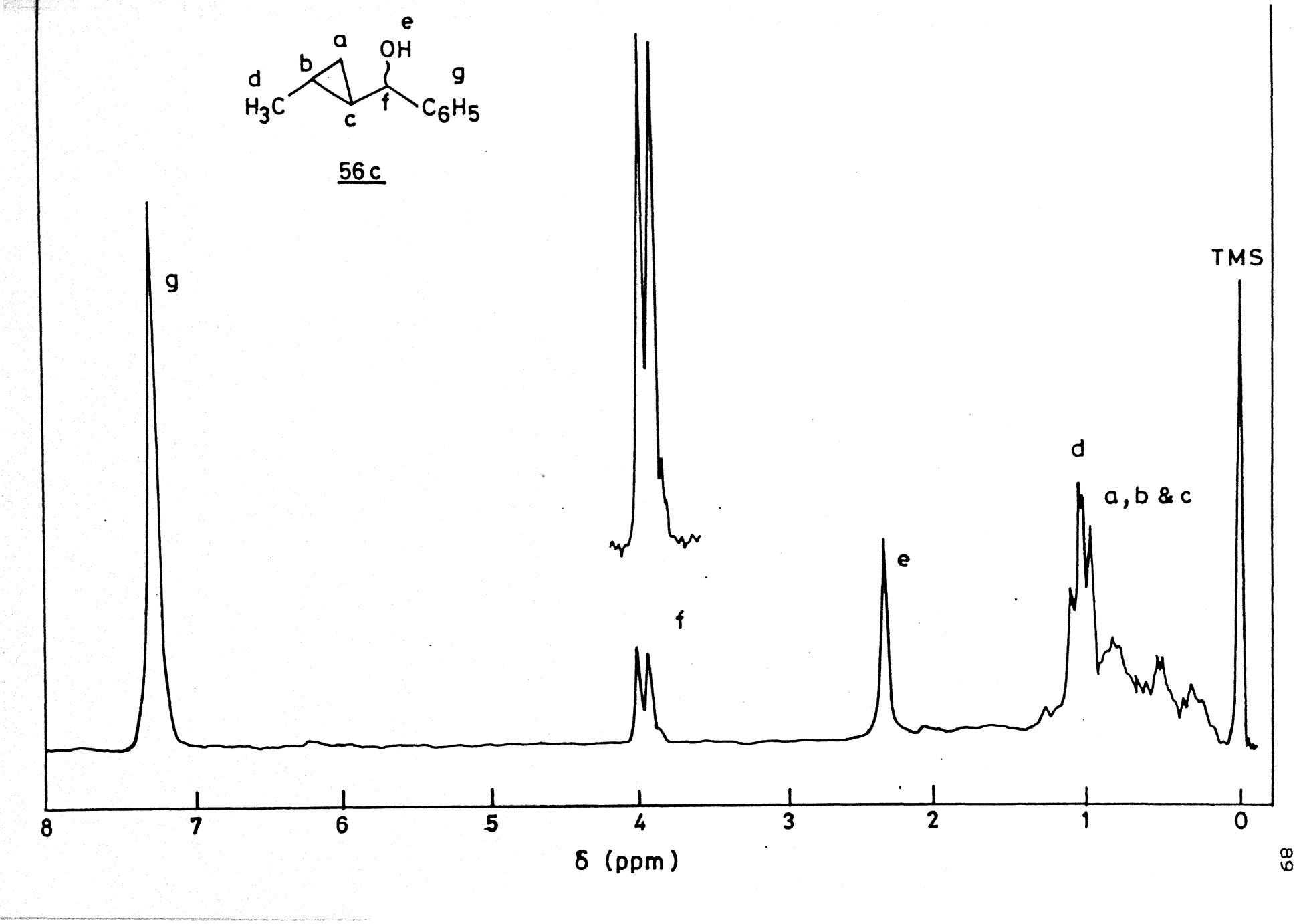
c n = 3, R_3 = H

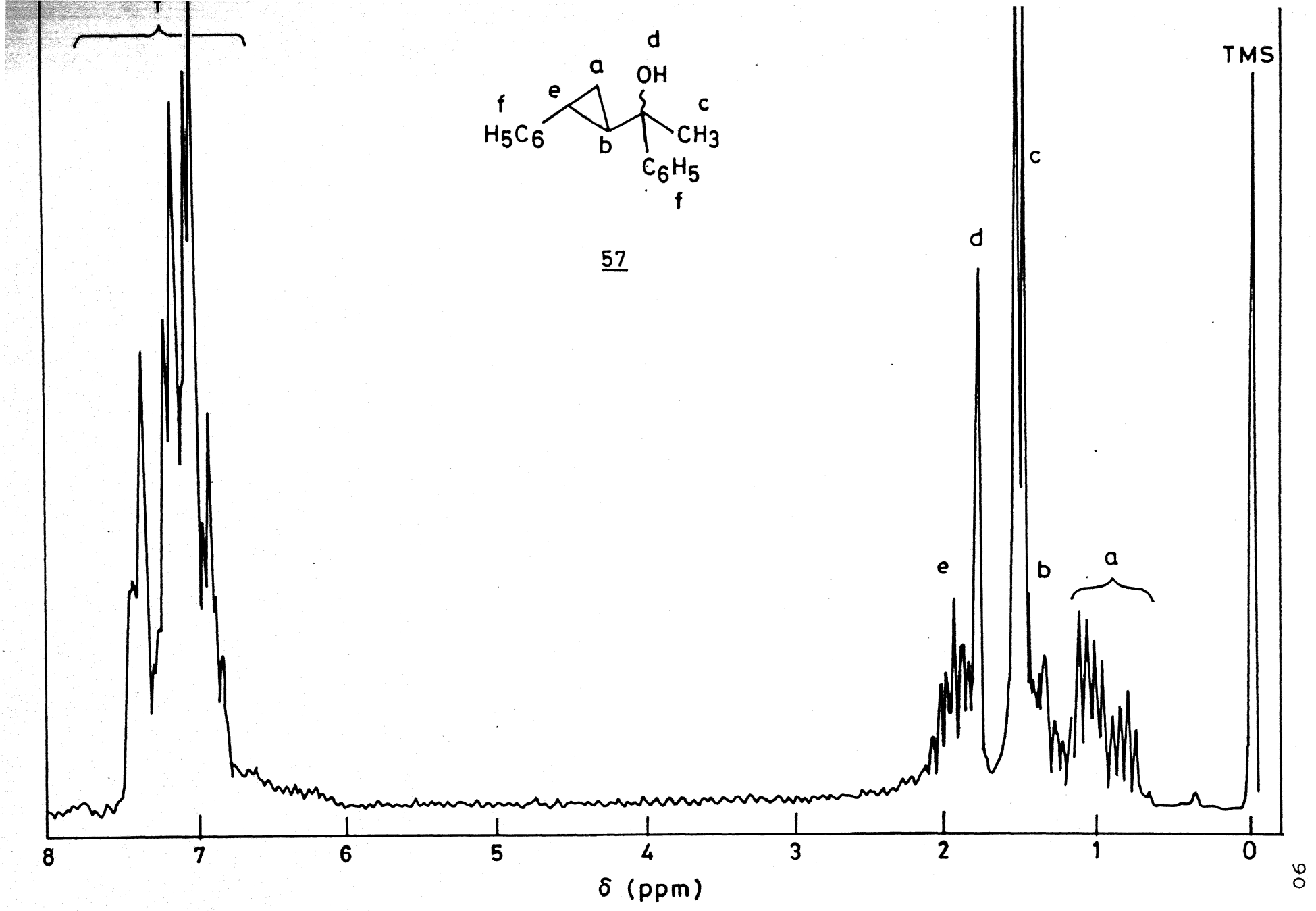
d n = 1, $R_3 = CH_3$

e n = 2, $R_3 = CH_3$.

Chart II.1

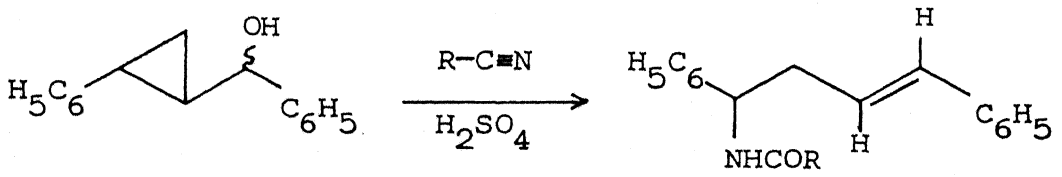
The cyclopropyl ketones 49a-c were a single product each of them being trans as per literature report[37] and also as shown by their ^{1}H NMR spectra (cf. experimental section). But the corresponding alcohols, as expected, were found to be a mixture of two stereoisomers. This also was evident from their ^{1}H NMR spectra. Thus, for example, compound 56b showed a triplet at δ 1.22 due to two overlapping doublets for the methyl groups and a broad multiplet from δ 3.2 to 3.8 for the CH-OH protons of the two stereoisomers. ^{1}H NMR spectrum (Fig. II.3) of 56c also showed two doublets of δ 1.03 for the methyl groups indicating it to be a mixture of two stereoisomers. Similarly compound 57 in its ^{1}H NMR spectrum (Fig. II.4) showed two singlets at δ 1.47 and 1.52 for methyl groups of the two stereoisomers. It was however, not possible to separate these stereoisomers by chromatography and


a
e
OH
b
d
g
H_3C
f
C_6H_5
c
56c
g
f
e
d
a, b & c
TMS
8
7
6
5
4
3
2
1
0
δ (ppm)


f
d
a
OH
e
f
c
H5C6
b
CH3
C6H5
f
57
TMS
c
d
e
b
a
8
7
6
5
4
3
2
1
0
δ (ppm)

also their exact ratio was difficult to find on the basis of their integration values from the ^{1}H NMR spectra. Substrates 58a-e (Chart II.1), on the other hand, were prepared from the corresponding allyl alcohols using Simmon-Smith cyclopropanation procedure as per the literature report.[38]

The reaction of cyclopropyl carbinol 56a with acetonitrile in the presence of conc. H_2SO_4 at 0°C for 30 min gave the amide 59a in 66% yield. Its IR spectrum showed absorption at 3325 (ν_{NH}),



56a

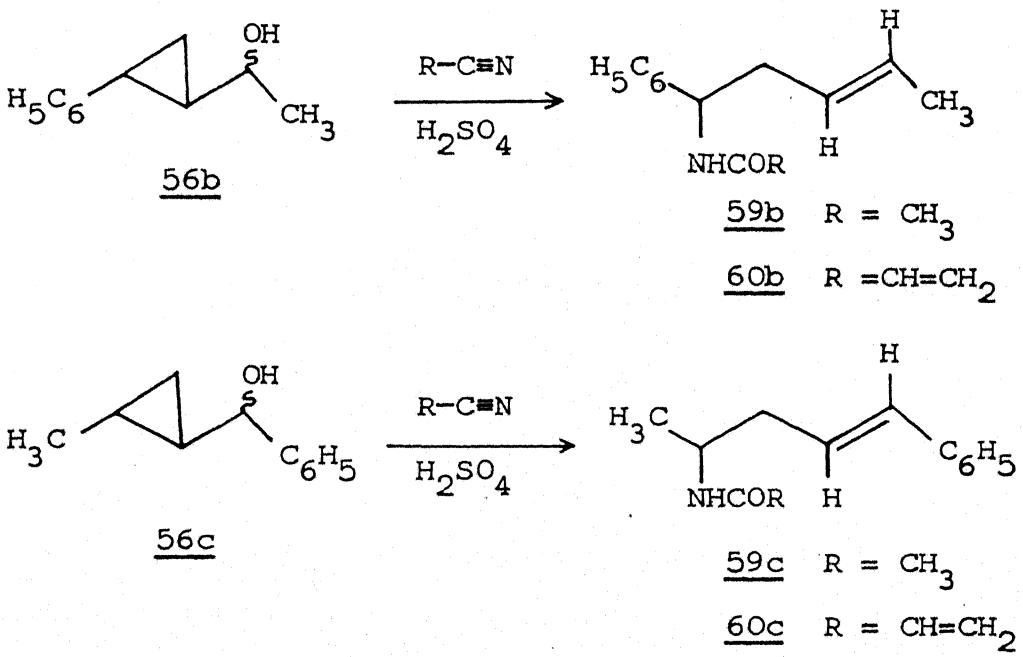
59a R = CH_3

60a R = $CH{=}CH_2$

1650 (ν_{C-NH}^{O}), 1610 ($\nu_{C=C}$) cm^{-1}. In its ^{1}H NMR spectrum absorptions at δ 1.92 (s, 3H, $COCH_3$), 2.6-2.78 (t, 2H, J=7 Hz, allylic CH_2), 4.94-5.22 (m, 1H, CH-NH), 5.68-6.48 (m, 2H, olefinic), 6.88-7.4 (m, 10H, aromatic) were observed. Further its mass spectrum showed M^+ peak at 265. The olefinic pattern in the ^{1}H NMR spectrum of 59a indicates a clear doublet for the proton PhCH=CH at δ 6.36 with J=16 Hz which is a typical characteristic coupling constant for a trans olefin. It is also clear from the olefinic

pattern that there is no contamination of any cis product, which is further evident from the appearance of only one singlet for $NHCOCH_3$. Similarly, the reaction of 56a with acrylonitrile again led to the formation of only E-isomer 60a as was evident from its spectral data (cf. experimental section). ^1H NMR spectrum of 60a showed a doublet at δ 6.34 for the proton Ph-CH=CH with J=15 Hz.

In a similar way reactions of other cyclopropyl carbinols viz., 56b-c with acetonitrile as well as with acrylonitrile gave amides 59b,c and 60b,c respectively (Scheme II.22). The structures of these amides were assigned on the basis of spectral and analytical data. Thus, IR spectrum of the amide 59b showed absorptions at 3330 (ν_{NH}), 1670 ($\nu_{C=O}$), 1610 ($\nu_{C=C}$) cm^{-1}. Its



56b

59b R = CH_3

60b R = $CH{=}CH_2$

56c

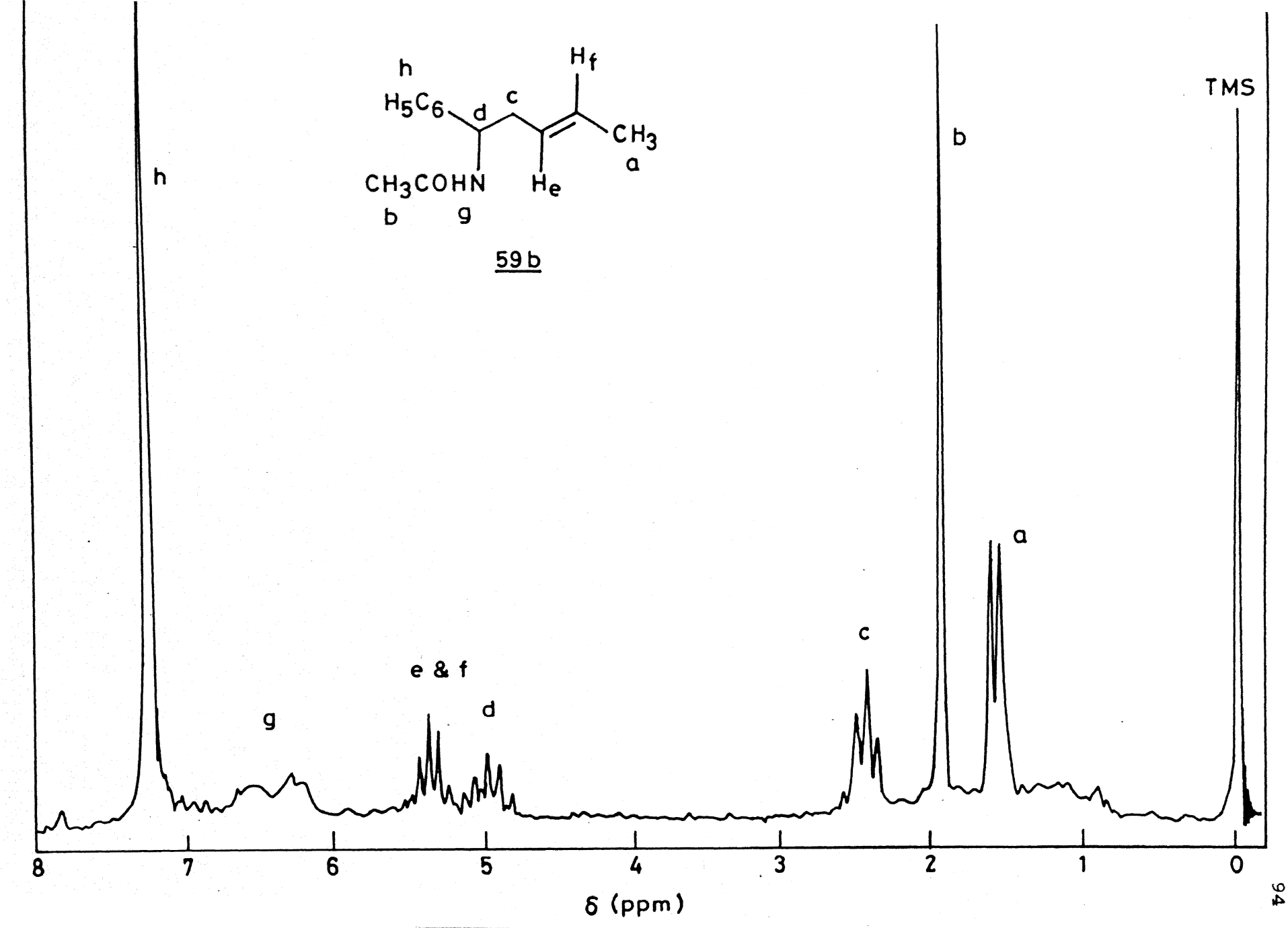
59c R = CH_3

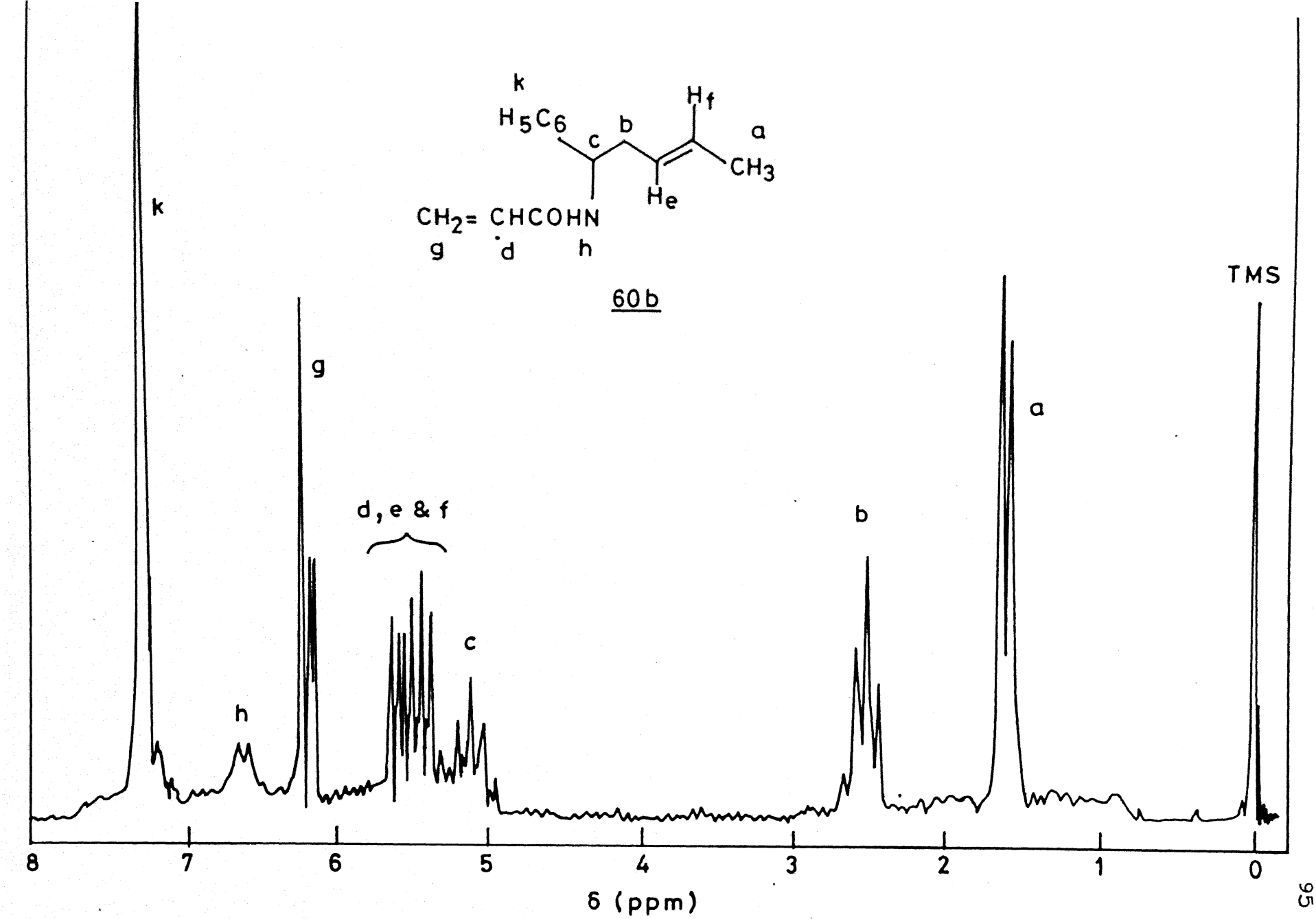
60c R = $CH{=}CH_2$

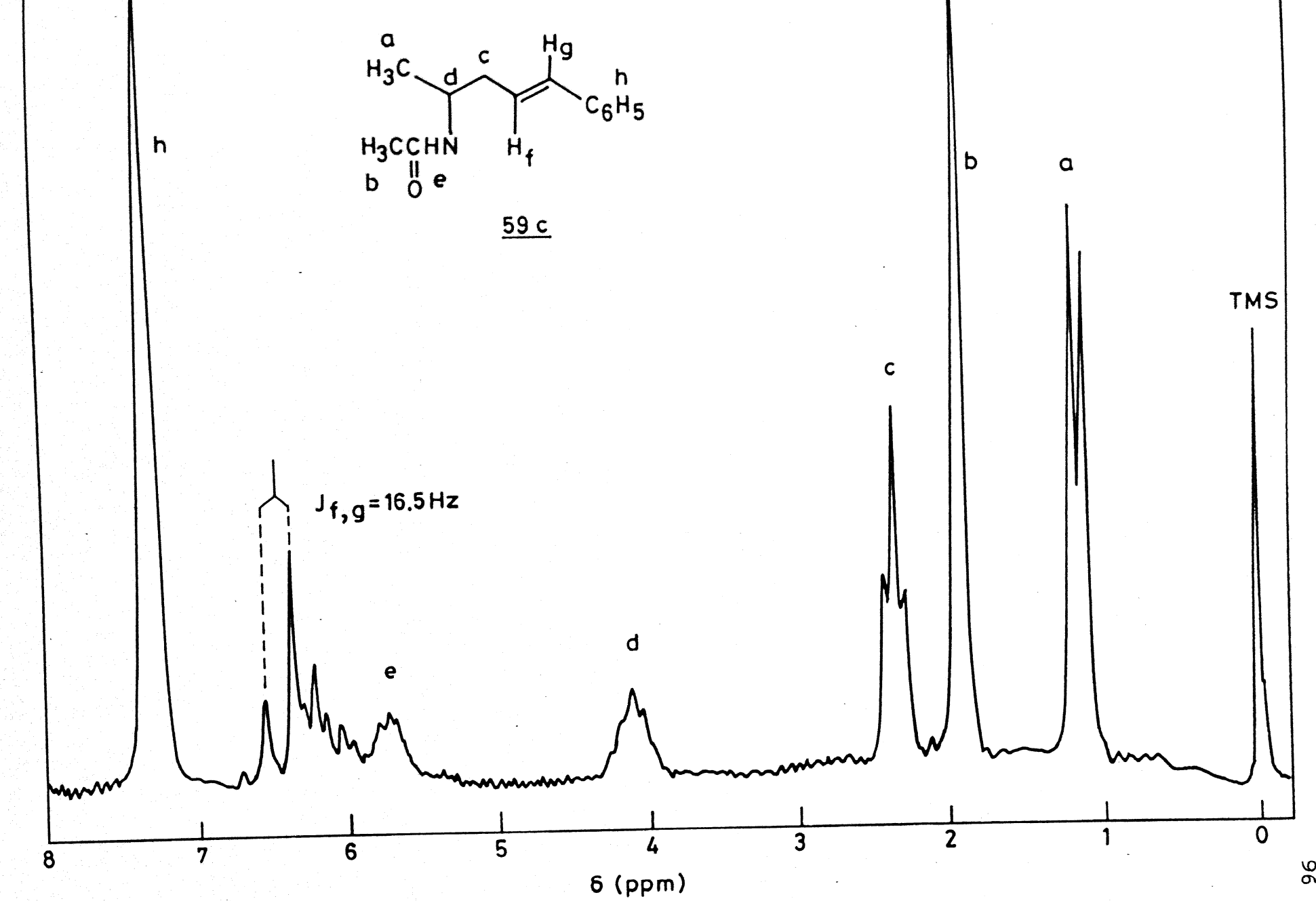
Scheme II.22

^{1}H NMR spectrum (Fig. II.5) showed absorptions at δ 1.56 (d, 3H, J=6 Hz, CH_3), 1.92 (s, 3H, $COCH_3$), 2.4 (t, 2H, J=7 Hz, allylic CH_2), 4.8–5.15 (m, 1H, C<u>H</u>–NH), 5.25–5.9 (m, 2H, olefinic), 6.15–6.75 (br, 1H, NH), 7.3 (m, 5H, aromatic). Further its mass spectrum showed M^+ peak at 203. The amide <u>60b</u> obtained from <u>56b</u> was also characterised on the basis of spectral (^{1}H NMR spectrum Fig. II.6) and analytical data (cf. experimental section). Although it is difficult from the olefin pattern in the ^{1}H NMR spectra of <u>59b</u> and <u>60b</u> to assess whether these amides are cis or trans, the presence of clear doublet for vinyl methyls and only one singlet for $NHCOC\underline{H}_3$ of <u>59b</u> indicate that these amides are trans products.

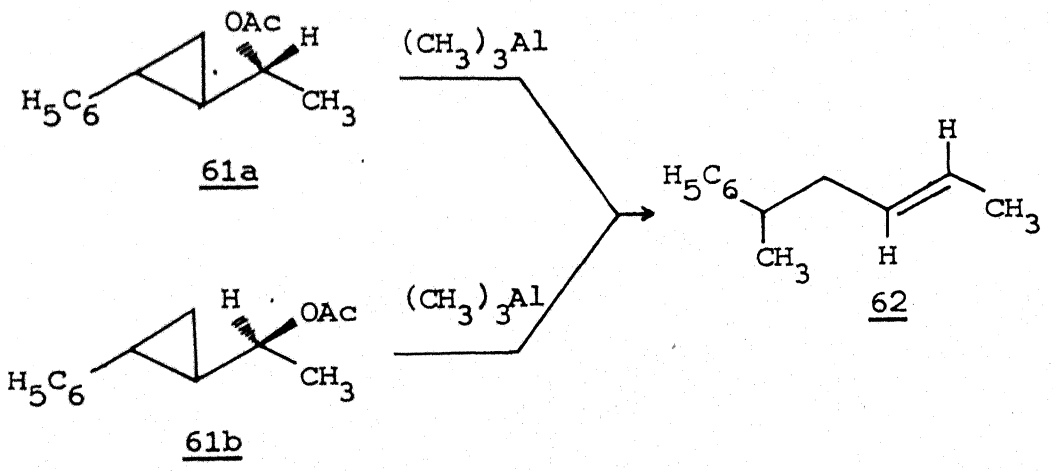
Similarly, the reaction of <u>56c</u> with acetonitrile in the presence of conc. H_2SO_4 gave the amide <u>59c</u> in 51% yield. Its IR spectrum showed absorptions at 3350 (ν_{NH}), 1650 ($\nu_{\overset{O}{\overset{\|}{C}}-NH}$) cm^{-1} and its ^{1}H NMR spectrum (Fig. II.7) showed absorptions of 1.15 (d, 3H, J=7.5 Hz, CH_3), 1.9 (s, 3H, $COCH_3$), 3.38 (t, 2H, J=6 Hz, allylic CH_2), 3.9–4.33 (m, 1H, C<u>H</u>–NH), 5.55–5.95 (br, 1H, NH), 6.0–6.7 (m, 2H, olefinic), 7.32 (m, 5H, aromatic). The olefinic pattern indicated a clear doublet for the proton $H_5C_6-C\underline{H}=CH$ at 6.47 with J=16.5 Hz which is characteristic of a trans olefin. Further its mass spectrum showed a M^+ peak at 203. The reaction of <u>56c</u> with acrylonitrile gave <u>60c</u> in 45% yield. The structure was assigned on the basis of spectral and analytical data (cf. experimental section). In the ^{1}H NMR spectrum, a clear doublet at δ 6.32 for $C_6H_5-C\underline{H}=CH$ with J=16.5 Hz indicated that the olefin obtained is a trans isomer.


h
H5C6
d
c
Hf
CH3
a
CH3COHN
He
b
g
59b
h
b
TMS
a
c
e & f
d
g
8
7
6
5
4
3
2
1
0
δ (ppm)


k
H_5C_6
c
b
H_f
a
CH_3
H_e
CH_2= CHCOHN
g d h
60b
TMS
k
g
d, e & f
c
h
b
a
8
7
6
5
4
3
2
1
0
δ (ppm)


a
H3C
d
c
Hg
h
C6H5
H3CCHN
b
O
e
Hf
59 c
h
b
a
TMS
c
Jf,g = 16.5 Hz
d
e
8
7
6
5
4
3
2
1
0
δ (ppm)

In view of the fact that the starting cyclopropyl carbinols were a mixture of two stereoisomers and the products i.e. amides formed in all these cases were trans, these studies relate to some interesting points. Thus, for example, according to literature reports, the ring opening of cyclopropyl carbinols with HBr or $HBr/ZnBr_2$, the bromide ion attacks on a carbon anti to the leaving group which determins the stereochemistry of the product i.e. E or a mixture of both E and Z. In the present study, the reactions of cyclopropyl carbions 56a-c with nitriles gave only E-olefins. It, thus, appears that the arrangement of antiperiplanarity is perhaps not the only requirement in the present cases. Interestingly, similar formation of E-olefins was also observed by Hayama et al.[39] who studied the alkylation of cyclopropyl acetates 61a and 61b with trialkylaluminium. They have also found that the formation of E-olefins is independent of the geometry of the starting acetates (Scheme II.23).

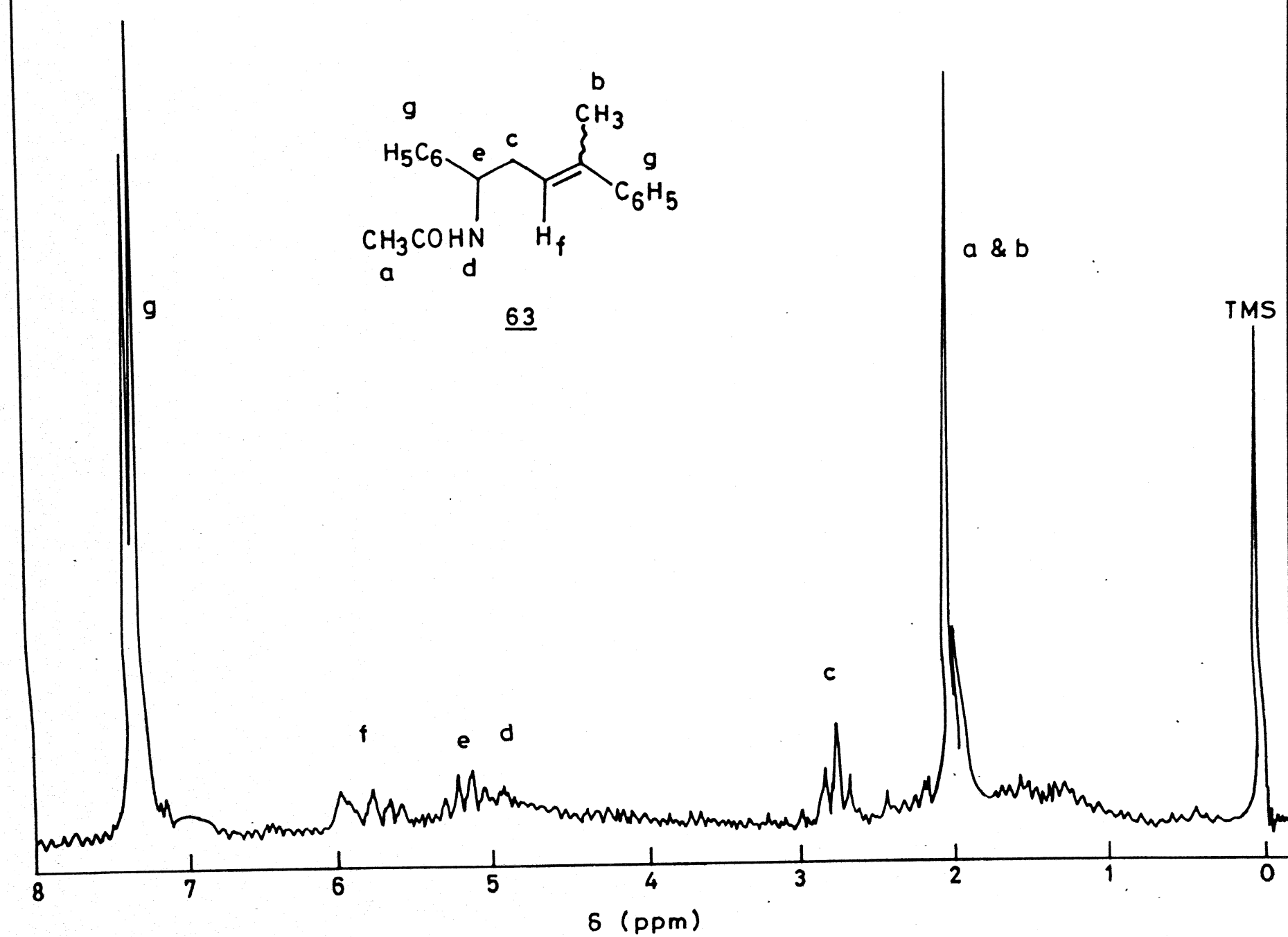


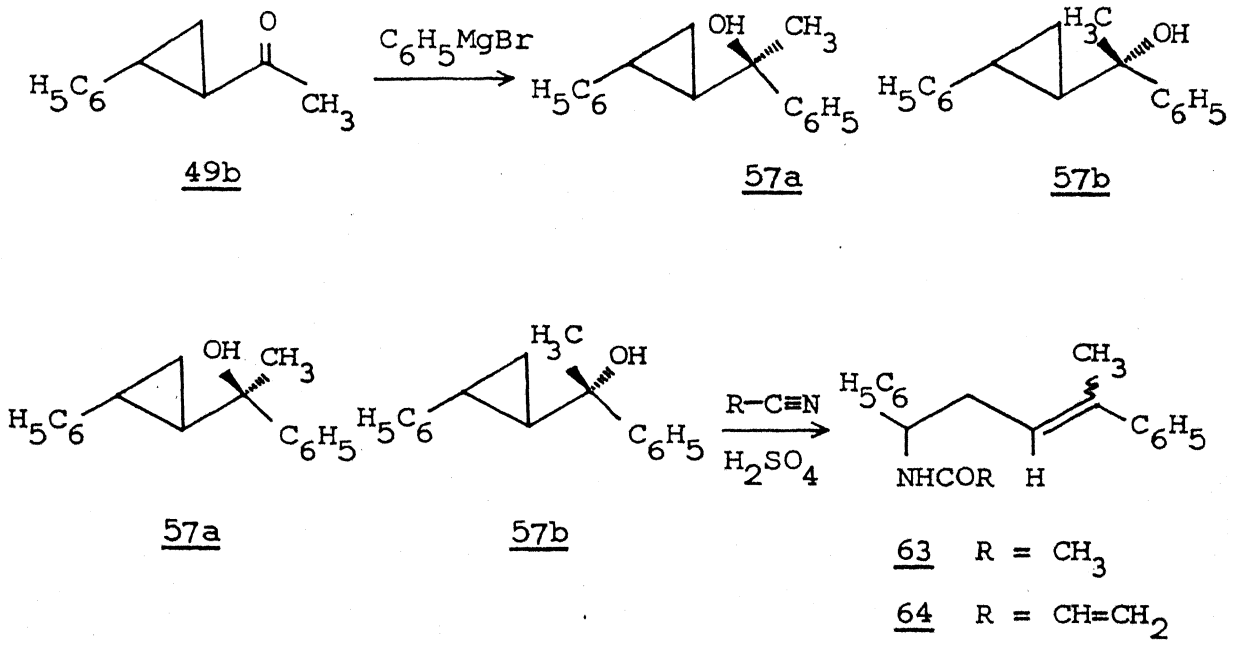
Scheme II.23

formation of trans-homoallyl cation F which when trapped by the nitrile, could give the trans amide. On the other hand, if the nucleophilic attack on the cyclopropane ring followed by its opening and the loss of water molecule takes place concurrently, then the isomer A should have given a trans product whereas the isomer B, a cis product. These results thus indicate that the formation of trans product is due to the fact that these reactions proceed according to S_N1 type mechanism. Also, nitrile is not a good nucleophile to take part in a S_N2 type mechanism.

Further, it was of interest to study the behaviour of tertiary cyclopropyl carbinol such as 57 towards nitriles under Ritter reaction condition. The substrate 57 which was prepared by the addition of PhMgBr to the cyclopropyl ketone 49b also gave a mixture of two stereoisomers (vide supra). Treatment of this mixture of stereoisomeric alcohols 57a and 57b with acetonitrile and acrylonitrile gave the corresponding amides 63 and 64 (Scheme II.25).

IR spectrum of the amide 63 showed absorptions at 3410 (ν_{NH}) and 1650 ($\nu_{\overset{O}{\overset{\|}{C}}-NH}$) cm^{-1} and its ^1H NMR spectrum (Fig. II.8) showed absorptions at 2.0 (s, 6H, CH_3 and $COCH_3$), 2.75 (t, 2H, J=7.5 Hz, CH_2), 4.4-5.35 (br, 1H, NH), 5.18 (m, 1H, C<u>H</u>-NH), 5.55-6.1 (m, 1H, vinylic), 7.3 and 7.35 (2s, 10H, aromatic). Interestingly, the vinyl methyl and N-acetyl methyl protons appear to have the same chemical shift. The integration of which is for six protons,


b
g
CH3
H5C6
e
c
g
C6H5
CH3CO HN
Hf
a
d
63
g
a & b
TMS
c
f
e
d
8
7
6
5
4
3
2
1
0
δ (ppm)

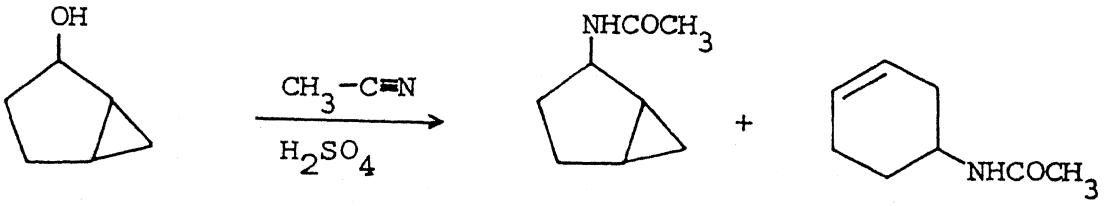


Scheme II.25

however. Although it is difficult from the spectral data to assess whether this amide 63 is cis or trans, it is expected, on the basis of earlier product analysis and reactions, that this is also a trans product as shown. Similarly, we expect, the structure of the amide 64 to be trans on the basis of spectral and analytical data (cf. experimental section).

In our study of Ritter reaction on cyclopropyl systems, we have also included bicyclic alcohols viz. bicyclo(3.1.0)hexan-2-ol (58a), bicyclo(4.1.0)heptan-2-ol (58b), bicyclo(5.1.0)octan -2-ol (58c), 5-methylbicyclo (3.1.0)hexan-2-ol (58d) and 6-methylbicyclo (4.1.0)heptan-2-ol (58e) (Chart II.1). The reaction of alcohol 58

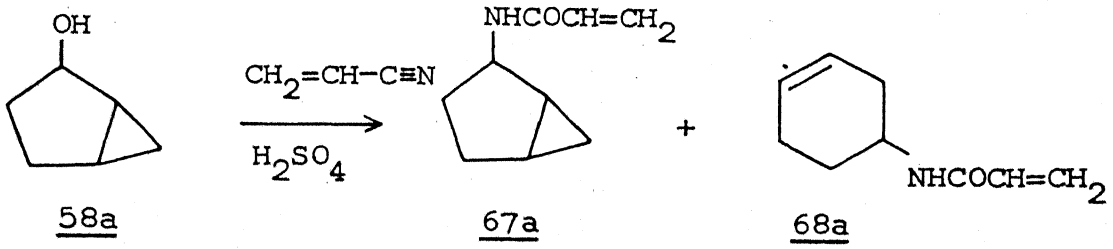
with acetonitrile in the presence of conc. H_2SO_4 at 0°C for 30 min. gave a mixture of amides 65a and 66a in 43% yield. The mixture



58a 65a 66a

was found to be homogeneous on tlc in a variety of solvent systems. The structures of these amides were assigned on the basis of spectral and analytical data. Thus, its IR spectrum showed absorptions at 3340 (ν_{NH}), 1660 (ν_{C-NH}^{O}) cm^{-1} and its ^1H NMR spectrum showed absorptions at δ 0.31 (m, 2H, cyclopropyl CH_2), 0.62-2.56 (m, 6H, CH_2 and cyclopropyl CH), 3.15-3.65 (br, 1H, NH), 4.06 (m, 1H, C<u>H</u>-NH), 4.25 (m, 1H, C<u>H</u>-NH), 5.65 (m, 2H, olefinic). Further, its mass spectrum showed a molecular ion peak at 139. The presence of cycloproyl ring protons at δ 0.31 (m) and olefinic protons at δ 5.65 (m) in the ^1H NMR spectrum clearly indicate that it is a mixture of two types of products. Further, the presence of multiplets at δ 4.06 and δ 4.25 for C<u>H</u>-NH protons of 66a & 65a respectively and a broad singlet for $NHCOCH_3$ at δ 2.0 confirm that it is a mixture of 65a and 66a. Gas chromatographic analysis showed that the mixture contains two products in the ratio of 50:50. Based on these spectral datails, it appears that the product is a mixture of two compounds 65a and 66a whose ratio based on ^1H NMR spectrum is also about 50:50.

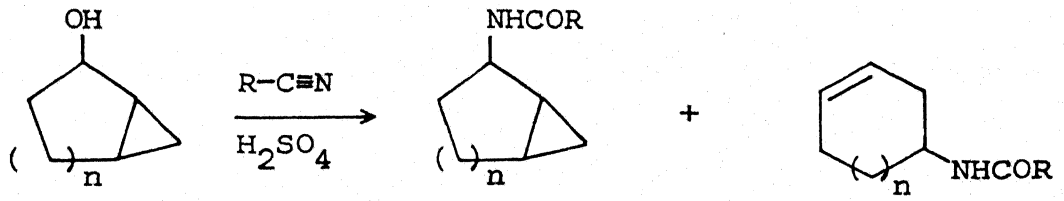
In a similar fashion, the reaction of cyclopropyl alcohol 58a with acrylonitrile gave once again a mixture of amides 67a and 68a. Separation of these products on tlc was found to be difficult in this case also. Its ^{1}H NMR spectrum showed absorptions at δ 0.36(m) for cyclopropyl protons and at δ 5.62(m) for olefinic protons. Also it showed multiplets at δ 4.28 and at



58a 67a 68a

δ 4.59 for CH-NH protons. Its gas chromatographic analysis showed it to be a mixture of two compounds in the ratio of 50:50 which is also evident from its ^{1}H NMR spectrum. These data confirm that the product is a mixture of 67a and 68a in the ratio of 50:50.

Similar reactions on bicyclic alcohols 58b,c with both acetonitrile and acrylonitrile once again gave a mixture of amides (Scheme II.26). Due to homogeneous nature of these amides on tlc



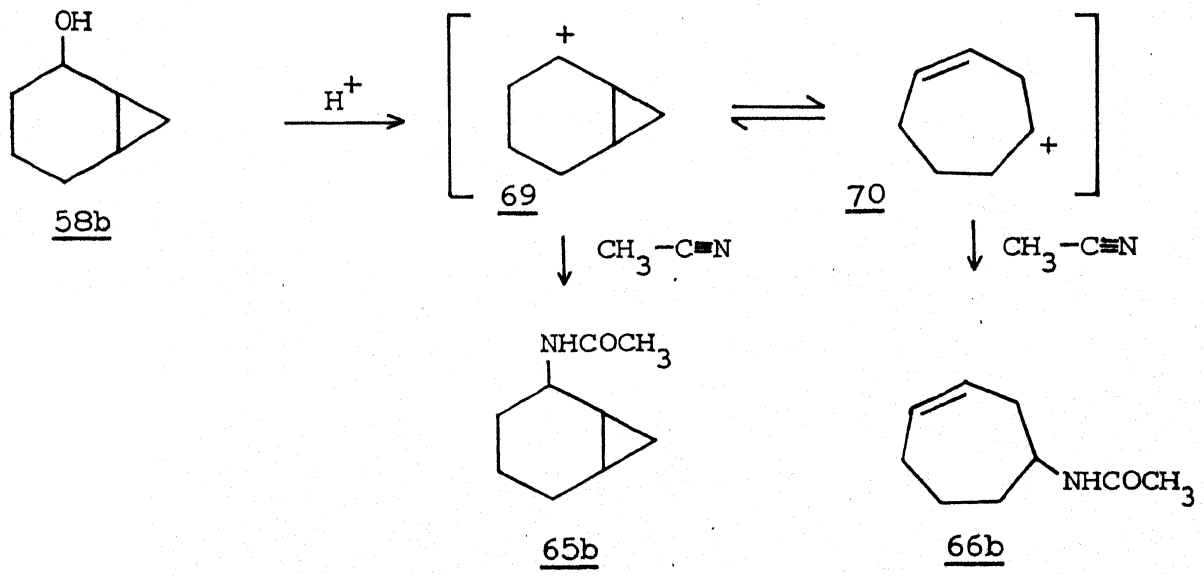
58b n = 2 65b,c 66b,c R = CH_3

c n = 3 67b,c 68b,c R = $CH{=}CH_2$

Scheme II.26

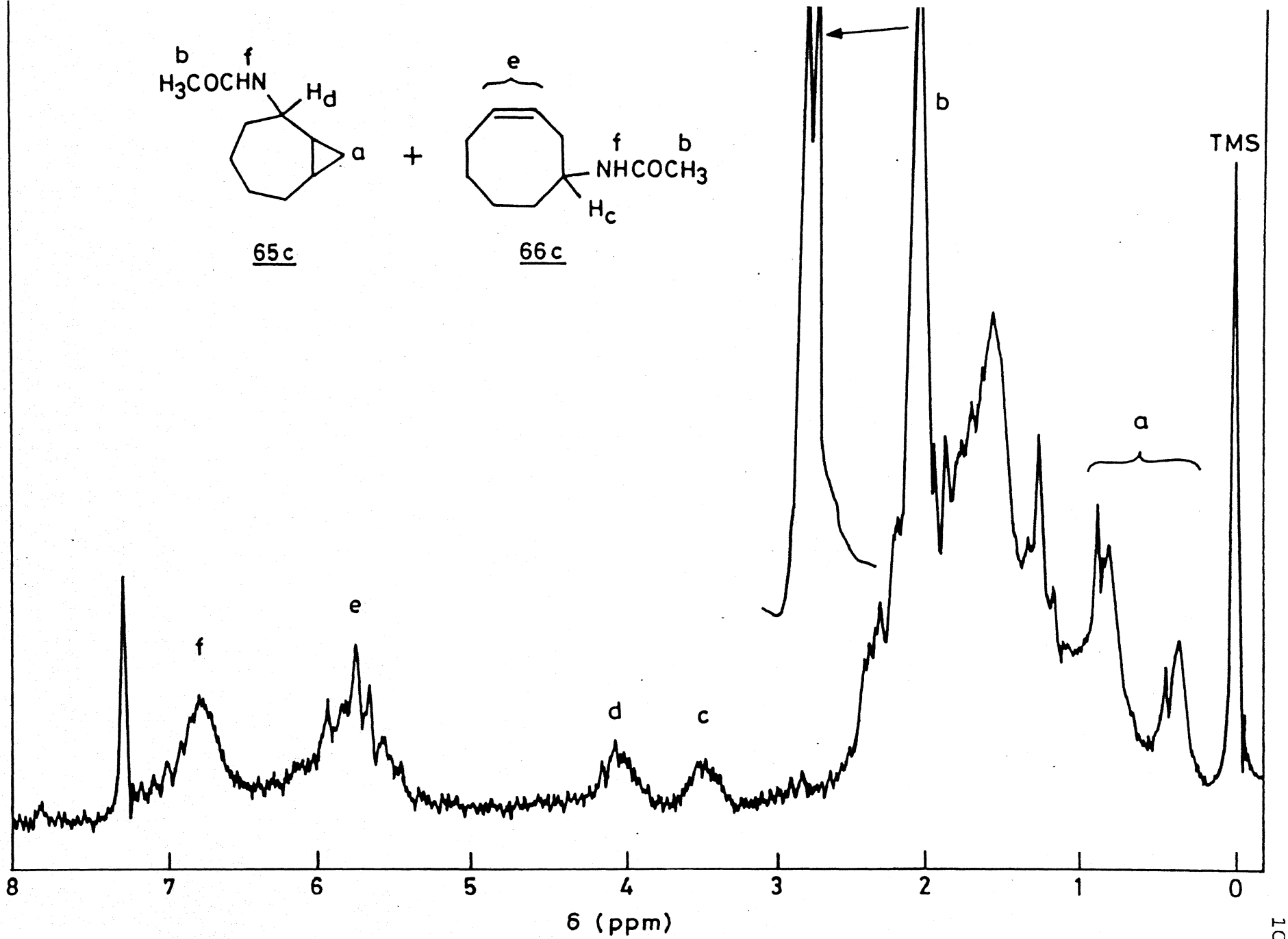
in a variety of solvent systems, separation of these amides were found to be difficult. Structures of these amides were assigned on the basis of spectral and analytical data (cf. experimental data). For example, ^{1}H NMR spectrum (Fig. II.9) of 65c and 66c showed absorptions at δ 0.36 (m, 1H, cyclopropyl CH_2), 0.55-2.5 (m, 11H, CH_2 and cyclopropyl CH), 2.05 (br, s, 3H, $COCH_3$) 3.28-3.7 (m, 1H, C<u>H</u>-NH), 3.8-4.25 (m, 1H, C<u>H</u>-NH), 5.36-6.25 (m, 2H, olefinic), 6.45-7.1 (br, 1H, NH). On the basis of ^{1}H NMR spectra and gas chromatographic analysis, the ratio of these amides, were confirmed. Thus,58b with both acetonitrile and acrylonitrile gave 45:55 mixture of the respective amides. On the other hand 58c with both acetonitrile and acrylonitrile gave 50:50 mixture of the respective amides.

A plausible mechanism for the formation of products is shown in Scheme II.27. For example, initial protonation of 58b



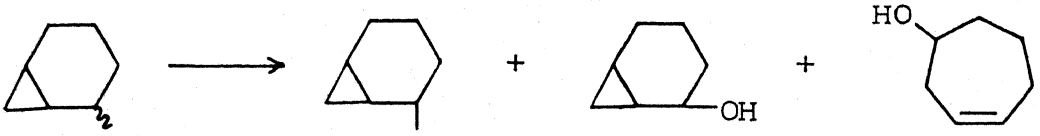
58b 69 70 65b 66b

Scheme II.27


b f
H3COCHN
Hd
a
+
e
f b
NHCOCH3
Hc
65c
66c
b
TMS
a
f
e
d
c
8
7
6
5
4
3
2
1
0
δ (ppm)

followed by loss of water leads to the formation of cyclopropylcarbinyl cation 69 which is in equilibrium with the ring opened homoallyl cation 70. The presence of excess of nitrile in the reaction medium which makes it react either with 69 or with 70 to lead to the formation of two amides 65b and 66b (Scheme II.27).

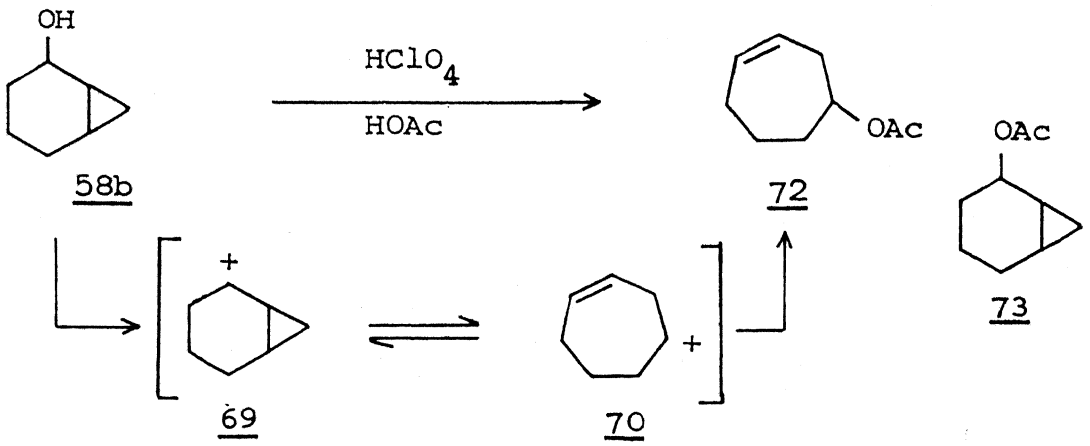
There is some precedent in the literature also where solvolytic studies have resulted in similar type of observation. For example, temperature dependent NMR studies reported by Olah et al.[41] indicate the formation of cyclopropylcarbinyl cation at low temperature from bicyclic (n.1.0) alcohols in the presence of super acids which undergoes ring opening on raising the temperature, to give a homoallyl cation. Fredrich et al.[42] have reported the hydrolysis of bicyclo(4.1.0)heptyl 3,5-dinitrobenzoate 71 where it gave a mixture of products. He also reported[26] the perchloric



71

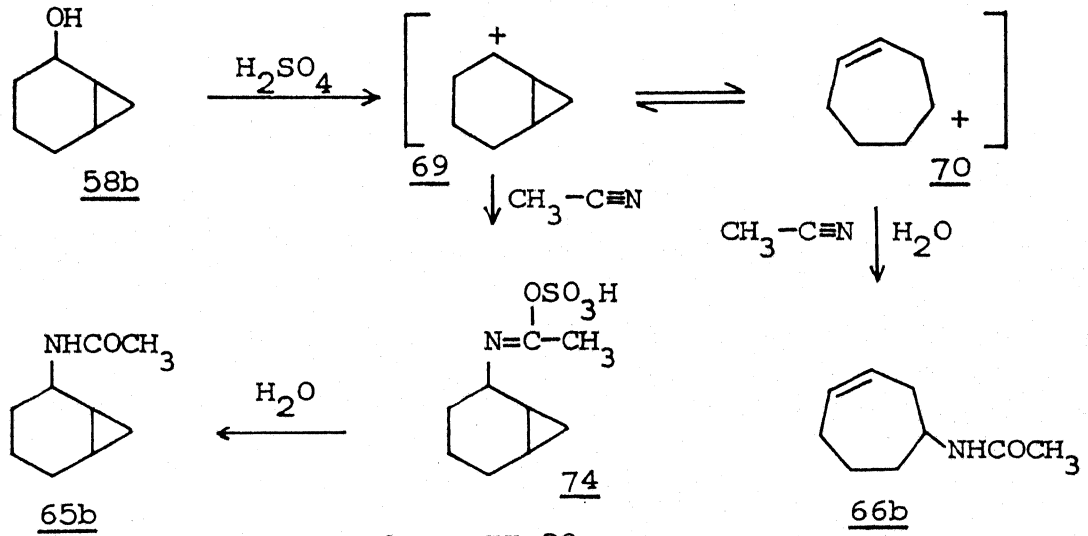
acid catalyzed acetolysis of bicyclo(4.1.0)heptan-2-ol (58b). It provides primarily the homoallyl acetate 72 a product of thermodynamic control, via repeated reionization of any initially formed bicyclic acetate 73, a product of kinetic control (Scheme II.28).

In the present study the cyclopropylcarbinyl cation 69 (Scheme II.29) upon the attack of a nitrile would give the intermediate 74 which upon work up would give the amide 65b. Now the



Scheme II.28

cation 69 could open up to form a homoallyl cation 70 which would eventually lead to the formation of amide 66b. Only if the intermediate 74 (a kinetically controlled product in an analogous manner as mentioned above) reverts back to the cation 69, then the amide 66b (a rerranged one) would form in major amount. However our

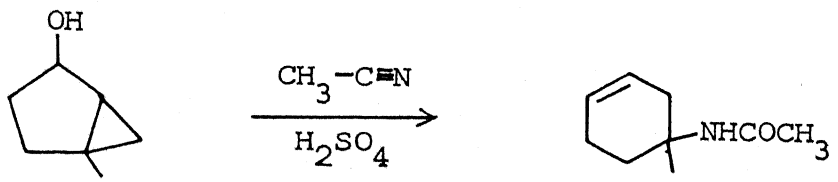


Scheme II.29

observation is that the two amides 65b and 66b are formed in the ratio of 45:55 in this reaction clearly indicating that the

intermediate 74 does not revert back to the cation 69 under the present reaction conditions.

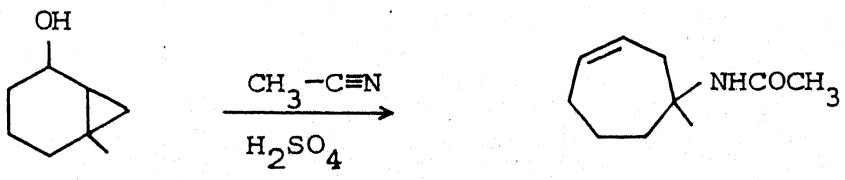
Interstingly, when the bicyclic alcohols 58d,e were treated with acetonitrile under similar conditions as above, the more of the rearranged amides were formed. Thus the reaction of the bicyclic alcohol 58d with acetonitrile at 0°C to 15 min gave 78% yield of the amide 66d. Its IR spectrum showed absorptions at 3440 (ν_{NH}),



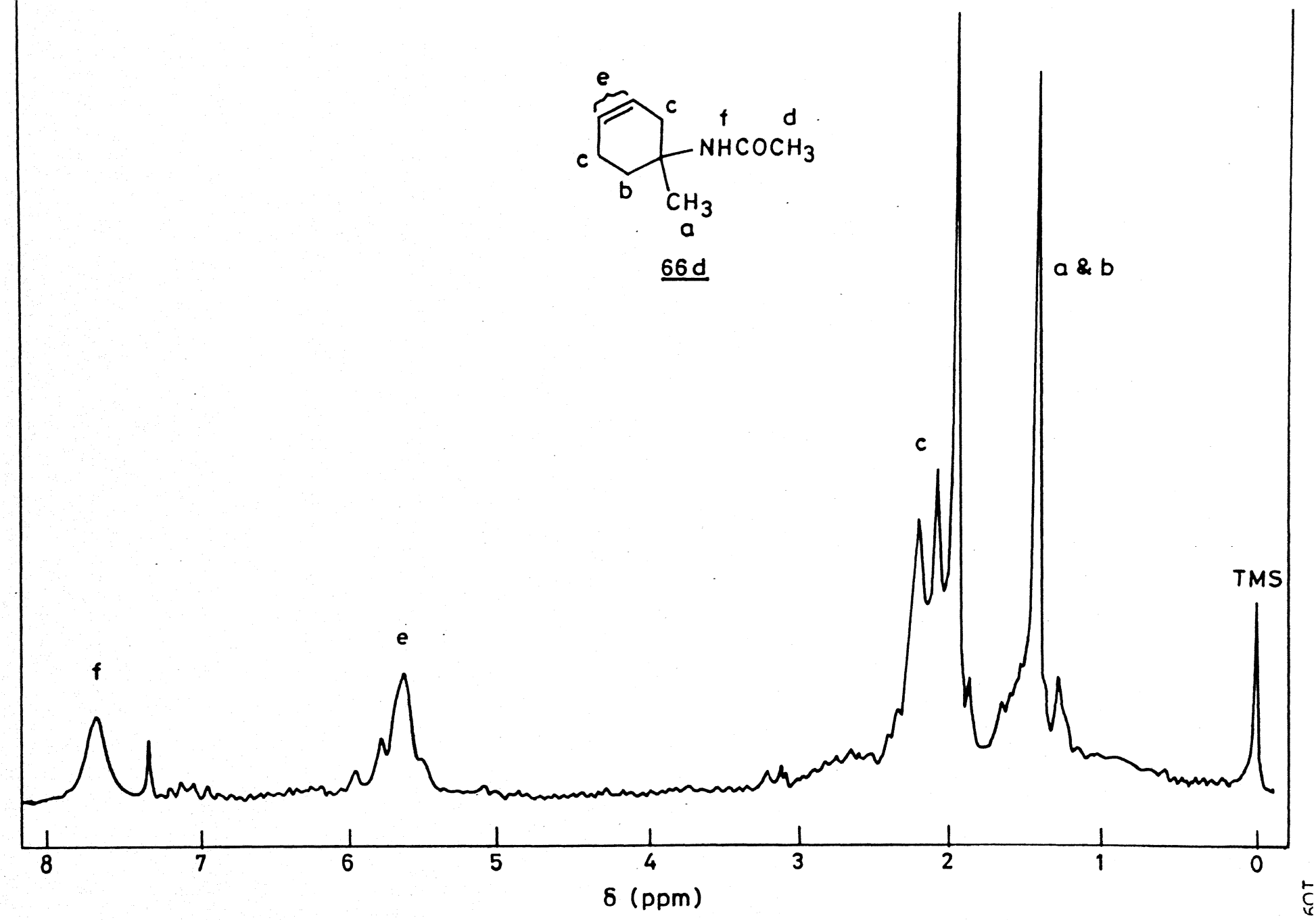
58b 66b

1665 (ν_{C-NH}^{O}) cm^{-1} and its ^1H NMR spectrum (Fig. II.10) showed absorptions at δ 1.4 (s, 3H, CH_3), 1.98 (s, 3H, $NHCOCH_3$), 1.8–2.5 (m, 6H, CH_2), 5.35–6.0 (m, 2H, olefinic), 7.5–7.9 (br, 1H, NH). Further its mass spectrum showed a M^+ peak at 153. Moreover, the gas chromatographic analysis showed that it is a single product. These data confirm the structure assigned to the amide 66d.

On the other hand, the reaction of 58e with acetonitrile at for 1 h gave 18% yield of the amide 66e. The structure was



58e 66e


e
c
f
d
NHCOCH3
c
b
CH3
a
66d
a & b
c
TMS
f
e
8
7
6
5
4
3
2
1
0
δ (ppm)

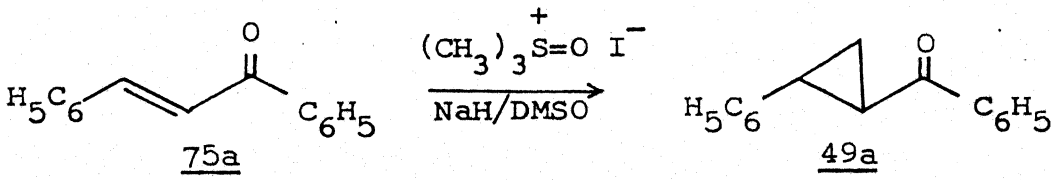
assigned on the basis of spectral and analytical data (cf. experimental section). Further gas chromatographic analysis also showed that it is a single compound.

Thus, the present study could be effectively used for the preparation of γ-keto amino derivatives and homoallyl amino derivatives from cyclopropyl ketones and cyclopropyl carbinols respectively by keeping appropriate substitutions to stabilise the carbocations formed after the cyclopropane ring opening.

II.3 Experimental

The details of the instruments used are the same as described in section I.3. GC analyses were done on a Shimadzu 9A gas chromatograph (using SE-30 column). The solvents used were dried in the same manner as described in section I.3. Acrylonitrile was dried by refluxing over CaH_2 and then it was distilled prior to use. Dimethyl sulphoxide was dried by distilling over CaH_2 and storing over molecular sieves Type 4A.

Preparation of trans-1-benzoyl-2-phenylcyclopropane (49a)

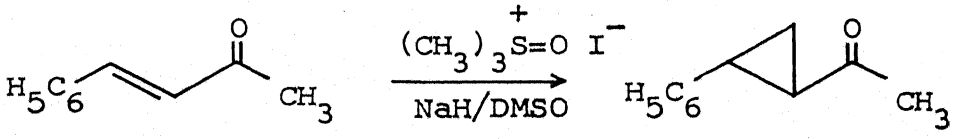


75a 49a

To a mixture of NaH (260 mg, 5.3 mmol, 50% dispersion in oil)

and trimethylsulphoxonium iodide (1.18 g, 5.3 mmol) was added slowly DMSO (5 mL) under nitrogen atmosphere with ice-water cooling. The reaction mixture was stirred for 20 min (till the evolution of H_2 gas ceased) at room temperature and then recooled to 10°C. Trans-1,3-diphenyl-2-propenone (75a) (1.04 g, 5 mmol) in DMSO (3 mL) was slowly introduced during 15 min and the resulting mixture was then stirred at room temperature for 3 h. After addition of cold water (20 mL), the mixture was extracted with ether (3 x 25 mL), washed with water (2 x 10 mL) brine (10 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent followed by recrystallization of the oily residue from pet. ether gave 49a. Yield 1 g (90%) m.p. 47-49°C (lit.[36] m.p. 45.5-50°C).

Preparation of trans-1-acetyl-2-phenylcyclopropane (49b)



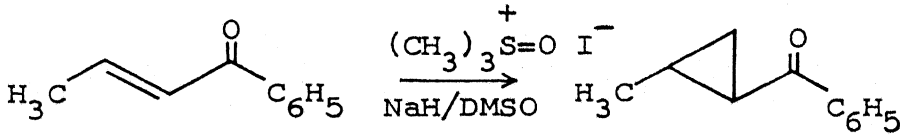
75b 49b

Following the above described procedure the reaction of trans-4-phenyl-3-buten-2-one (75b) (700 mg, 4.8 mmol) with trimethylsulphoxonium iodide (1.16 g, 5.3 mmol) and NaH (264 mg, 5.5 mmol) in DMSO (10 mL) at 10° for 20 min gave 1-acetyl-2-phenylcyclopropane (49b). Yield 500 mg (65%), b.p. 125°C/2 mm (lit[37], b.p. 118°C/2 mm).

IR spectrum ν_{max} ($CHCl_3$): 1690 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.2 (m, 1H, cyclopropyl CH_2), 1.5 (m, 1H, cyclopropyl CH_2), 2.05 (m, 1H, C<u>H</u>-C_6H_5), 2.15 (s, 3H, $COCH_3$), 2.35 (m, 1H, COC<u>H</u>), 6.9-7.3 (m, 5H, aromatic).

Preparation of trans-1-benzoyl-2-methylcyclopropane (<u>49c</u>)



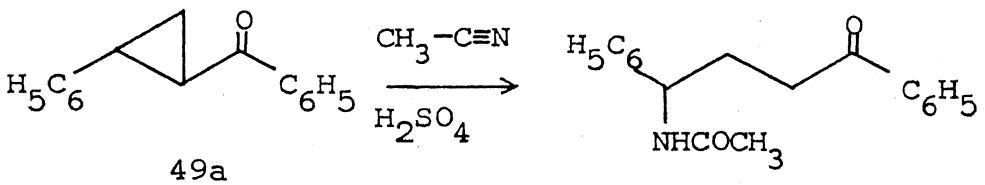
<u>75c</u> <u>49c</u>

Trans-1-phenyl-2-buten -1-one (<u>75c</u>)[43] (650 mg, 4.45 mmol), trimethylsulphoxonium iodide (1.07 g, 4.86 mmol) and NaH (256 mg, 5.12 mmol) in DMSO (10 mL) at 10°C for 15 min gave 1-benzoyl-2-methylcyclopropane (<u>49c</u>). Yield 530 mg (74%), b.p. 105-110°C/2.5 mm, (lit[37], b.p. 128°C/18 mm).

IR spectrum ν_{max} ($CHCl_3$): 1660 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.05 (d, 3H, J=6 Hz, CH_3), 0.8 (m, 1H, cyclopropyl CH_2), 1.3 (m, 2H, cyclopropyl CH_2 and C<u>H</u>-CH_3), 2.2 (m, 1H, COC<u>H</u>), 7.1-8.1 (m, 5H, aromatic).

Preparation of 4-N(acetyl)amino-1,4-diphenylbutan-1-one (51a)



49a

51a

To conc. H_2SO_4 (0.22 mL, 4.0 mmol) at 0°C was added slowly acetonitrile (1 mL) and stirred for 30 min. A solution of cyclopropyl ketone 49a (222 mg, 1.0 mmol) in acetonitrile (1.0 mL) was introduced slowly during 15 min. After 6 h of stirring at 0°C, the reaction mixture was poured into crushed ice (15 g) and neutralized with satd. aq. $NaHCO_3$ solution. Extraction with ethyl acetate (3 x 15 mL) and washing the extract with water and brine and then drying it with anhydrous Na_2SO_4 and evaporation of the solvent gave a crude solid. This on recrystallization with ethyl-acetate-ether mixture gave white crystals of 51a. Yield 0.117 g (64%), m.p. 187°C.

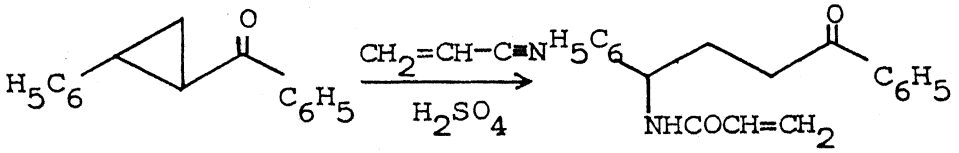
IR spectrum ν_{max}(KBr): 3260 (NH), 1675 (C=O), 1640 (C(=O)-NH) cm

^{1}H NMR spectrum(DMSO D_6): δ 1.84(s,3H,$COCH_3$),1.88-2.2(m,2H, CH_2-CH-Ph), 3.07 (t, J=6 Hz, $COCH_2$), 4.68-4.92 (m, 1H, CH-NH), 7.08-7.98 (m, 10H, aromatic), 8.2 (m, 1H, NH).

Mass spectrum, m/e (rel.int.): 281 (35, M^+), 248 (65, M^+-$COCH_3$), 162 (35 M^+-$PhCOCH_2$), 161 (13, M^+-$PhCOCH_3$).

Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.96. Found: C, 76.54; H, 6.52; N, 4.79.

Preparation of 4-N(acrylyl)amino-1,4-diphenyl-1-butanone (52a)



49a 52a

The reaction was carried out following the above described procedure with 49a (222 mg, 1 mmol) using acrylonitrile in the place of acetonitrile and for a period of 5 h at 0°C. The crude product obtained after work up was recrystallized from ethyl acetate-dichloromethane-pet. ether mixture to give the amide 52a. Yield 0.160 g (55%), m.p. 199°C (d).

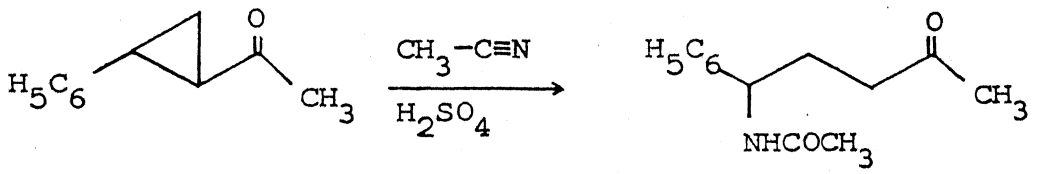
IR spectrum ν_{max}(KBr): 3330 (NH), 1680 (C=O), 1655 (C(=O)-NH), 1625 (C=C) cm^{-1}.

^1H NMR spectrum (DMSO D_6): δ 1.92-2.34 (m, 2H, CH_2), 3.02 (t, 2H, J=6 Hz, $COCH_2$), 4.8-5.12 (m, 1H, CH-NH), 4.5-6.46 (m, 3H, vinylic), 7.02-8.04 (m, 10H, aromatic), 8.42 (br, 1H, NH).

Mass spectrum, m/e (rel.int.): 293 (35, M^+), 238 (63, M^+ - $COCH=CH_2$), 222 (35, $M^+-CH_2=CHCONH_2$), 174 (43, $M^+-PhCOCH_2$).

Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.81; H, 6.48; N, 4.28. Found: C, 77.75; H, 6.52; N, 4.58.

Preparation of 5-N(acetyl)amino-5-phenylpentan-2-one (51b)



49b 51b

Treatment of 49b (100 mg, 0.625 mmol) with CH_3CN (3 mL) and conc. H_2SO_4 (0.13 mL, 2.5 mmol) at 0°C for 6 h gave 51b as a thick liquid after purification by preparative thin layer chromatography [eluent, benzene:acetone (80:20)]. Yield 75 mg (55%).

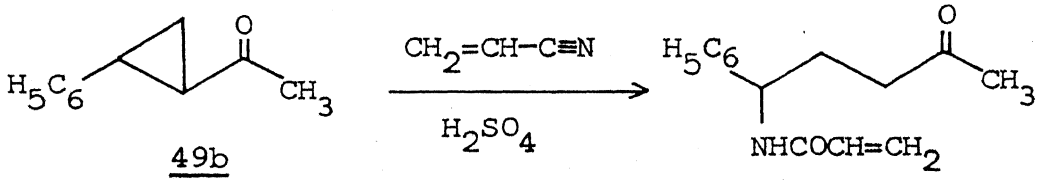
IR spectrum $\nu_{max}(CHCl_3)$: 3340 (NH), 1710 (C=O), 1660 (C(=O)-NH) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.95 (s, 3H, $NHCOCH_3$), 2.15 (s, 3H, $COCH_3$), 1.9–2.2 (m, 2H, CH_2), 2.6 (t, 2H, J=6 Hz, $COCH_2$), 4.8–5.2 (m, 1H, CH-NH), 6.45–6.9 (br, 1H, NH), 7.18 (m, 5H, aromatic).

Mass spectrum, m/e (rel.int.): 219 (25, M^+), 176 (44, M^+-COCH_3), 161 (14, $M^+-NHCOCH_3$), 106 (100).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.23; H, 7.76; N, 6.39. Found: C, 71.15; H, 7.46; N, 6.05.

Preparation of 5-N(acrylyl)amino-5-phenylpentan-2-one (52b)



49b

52b

Following the above described procedure, with 49b (100 mg, 0.625 mmol) using acrylonitrile at 0°C for 5 h gave 52b which was purified by preparative thin layer chromatography[eluent benzene: acetone (80:20)]. Yield 65 mg (45%), m.p. 90–92°C.

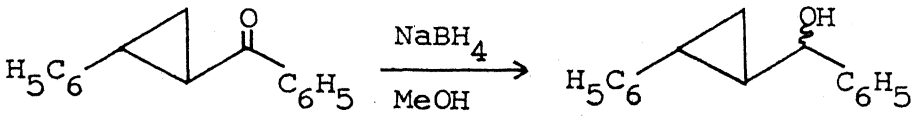
IR spectrum ν_{max}(KBr): 3320 (NH), 1710 (C=O), 1660 (C–NH), 1625 (C=C), 1605 (C=C) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 2.2 (s, 3H, $COCH_3$), 2–2.35 (m, 2H, CH_2), 2.6 (t, 2H, J=6 Hz, $COCH_2$), 5–5.3 (m, 1H, CH–NH), 5.65 (dd, 1H, J=9 Hz, 4.5 Hz, vinylic), 6.2 (m, 2H, vinylic), 6.55–6.85 (br, 1H, NH), 7.35 (m, 5H aromatic).

Mass spectrum , m/e (rel.int.): 231 (36, M^+), 176 (34, $M^+-COCH=CH_2$), 161 (30, $M^+-NHCOCH=CH_2$), 106 (85), 55 (100, $O=\overset{+}{C}-CH=CH_2$)

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.73; H, 7.36; N, 6.06. Found: C, 72.53; H, 7.52; N, 6.16.

Preparation of trans-1(1-hydroxybenzyl)-2-phenylcyclopropane (56a)



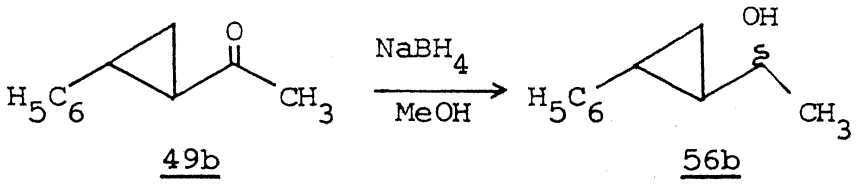
49a 56a

To a solution of cyclopropyl ketone 49a (1.0 g, 4.5 mmol) in methanol (15 mL) at 0°C was added portionwise solid sodium borohydride (0.19 g, 5.0 mmol). The reaction mixture was stirred for 40 min at 0°C and then methanol was removed under reduced pressure. The residue was dissolved in dichloromethane (25 mL) washed with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulphate. Removal of the solvent gave the cyclopropyl carbinol 56a. Yield 0.998 g (99%).

IR spectrum ν_{max}(neat): 3400 (OH) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 0.72-1.16 (m, 2H, cyclopropyl CH_2), 1.24-1.60 (m, 1H, C<u>H</u>-CHOH), 1.80-2.10 (m, 1H, C<u>H</u>-C_6H_5), 2.24 (s, 1H, OH), 4.12 and 4.22 (2d, 1H, J=7 Hz, 6 Hz, C<u>H</u>-OH), 6.68-7.54 (m, 10H aromatic).

Preparation of trans-1(1-hydroxyethyl)-2-phenylcyclopropane (56b)



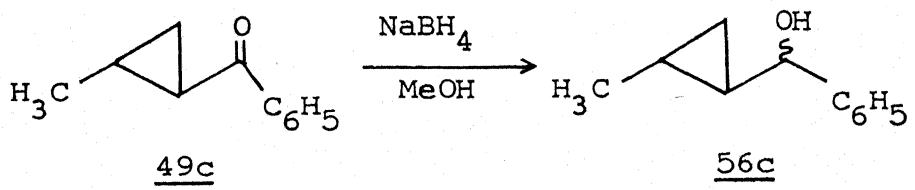
49b 56b

The reaction was carried out under the same condition as described above. Cyclopropyl ketone 49b (300 mg, 1.88 mmol) and $NaBH_4$ (80 mg, 2.1 mmol) in MeOH (10 mL) at 0°C for 1 h gave cyclopropyl carbinol 56b. Yield 280 mg (92%), b.p. 130°C/0.5 mm.

IR spectrum ν_{max}(neat): 3400 (OH) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 0.7–1.4 (m, 3H, cyclopropyl), 1.22 (t, 3H, CH_3), 1.5–2.0 (m, 1H, C<u>H</u>-C_6H_5), 3.2–3.8 (m, 1H, C<u>H</u>-OH), 6.7–7.4 (m, 5H, aromatic).

Preparation of trans-1(1-hydroxybenzyl)-2-methylcyclopropane (56c)



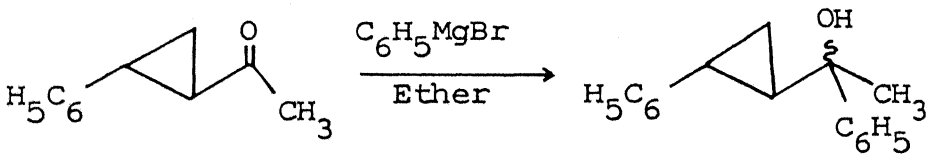
49c 56c

Following the above described procedure the reaction of cyclopropyl ketone 49c (160 mg, 1 mmol) and $NaBH_4$ (42 mg, 1.1 mmol) in MeOH (5 mL) at 0°C for 6 h gave cyclopropyl carbinol 56c. Yield 150 mg (93%), b.p. 125°/0.7 mm.

IR spectrum ν_{max}(neat): 3400 (OH) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 0.15–1.4 (m, 4H, cyclopropyl H), 1.03 (2d, 3H, CH_3), 2.35 (s, 1H, OH), 3.95 (d, J=7.5 Hz, CHOH), 7.25 (m, 5H, aromatic).

Preparation of trans-1(1-hydroxy-1-methylbenzyl)-2-phenylcyclopropane (57)



49b 57

Cyclopropyl ketone 49b (300 mg, 1.88 mmol) in ether (2 mL) was added slowly to phenylmagnesium bromide [prepared from bromobenzene (353 mg, 2.25 mmol) and magnesium (54 mg, 2.25 mmol)] at 0°C. The resultant mixture was stirred at room temperature for 3 h. Then it was decomposed with water (10 mL), satd. NH_4Cl (10 mL) and extracted with ether (3 x 20 mL). The combined organic layer was washed with water (10 mL), brine (10 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude product which was purified by column chromatography (alumina) [eluent, benzene:pet. ether (50:50)]. Yield 370 mg (83%).

IR spectrum ν_{max}(neat): 3440 (OH) cm^{-1}.

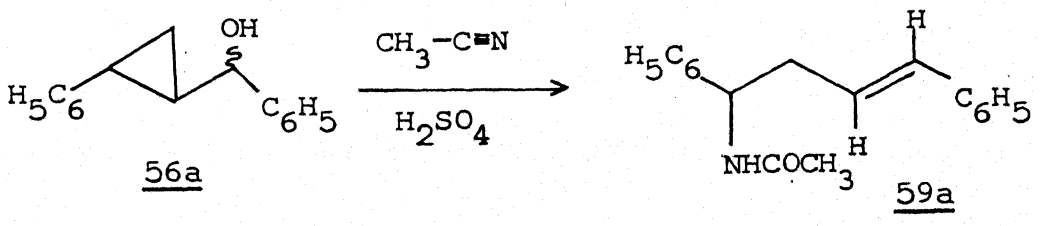
^{1}H NMR spectrum (CCl_4): δ 0.8 (m, 1H, cyclopropyl CH_2), 1.05 (m, 1H, cyclopropyl CH_2), 1.4 (m, 1H cyclopropyl CH), 1.47 and 1.52 (2s, 3H, CH_3), 1.75 (s, 1H, OH), 1.9 (m, 1H, $\underline{CH}$-C_6H_5), 6.5-7.5 (m, 10H, aromatic).

Mass spectrum, m/e (rel.int.): 221 (39, M^+-OH), 134 (100).

General procedure for the reaction of cyclopropyl carbinols with nitriles in the presence of conc. H_2SO_4

To 1.5 mmol of conc. H_2SO_4 at 0°C was introduced slowly 1.0 mL of nitrile and stirred for 30 min. A solution of 1 mmol of carbinol in 1.0 mL of nitrile was then added slowly at -10°C during 15 min. After stirring for additional 10 min, 20 g of ice was added to the reaction mixture and neutralized it with saturated solution of $NaHCO_3$. The aqueous layer was saturated with NaCl and extracted with ethyl acetate (3 x 15 mL). It was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and evaporated to obtain a crude product which was further purified.

Preparation of trans-1-N(acetyl)amino-1,4-diphenylbut-3-ene (59a)



56a 59a

The reaction of carbinol 56a (224 mg, 1 mmol) with acetonitri

gave the amide 59a. The crude product was recrystallized from $CHCl_3$-ether. Yield 175 mg (66%), m.p. 116-117°C (d).

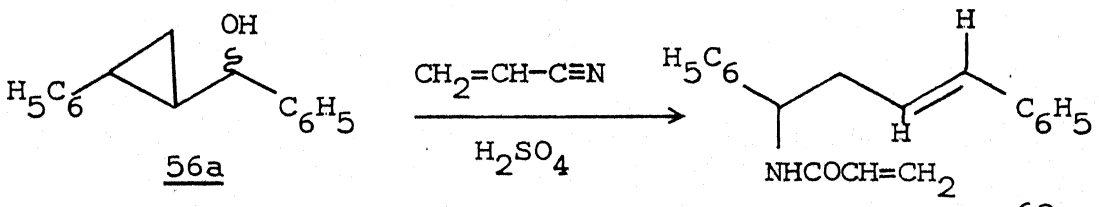
IR spectrum ν_{max}(KBr): 3325 (NH), 1650 (C=O-NH), 1610 (C=C) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.92 (s, 3H, $COCH_3$), 2.6-2.78 (t, 2H, J=7 Hz, allylic CH_2), 4.94-5.22 (m, 1H, CH-NH), 5.68-6.48 (m, 3H, J=16 Hz, olefinic and NH), 6.88-7.4 (m, 10H, aromatic).

Mass spectrum, m/e (rel.int.): 265(5, M^+), 222 (8, M^+-COCH_3), 207 (28, $M^+-NHCOCH_3$), 106 (100).

Anal. Calcd for $C_{18}H_{19}NO$: C, 81.51; H, 7.17; N, 5.28. Found: C, 81.40, H; 6.98, N; 5.21.

Preparation of trans-1-N(acrylyl)amino-1,4-diphenylbut-3-ene (60a)



56a 60a

The reaction of carbinol 56a (224 mg, 1 mmol) with acrylonitrile gave the amide 60a which was recrystallized from $CHCl_3$-Pet.ether. Yield, 169 mg (61%), m.p. 108°C.

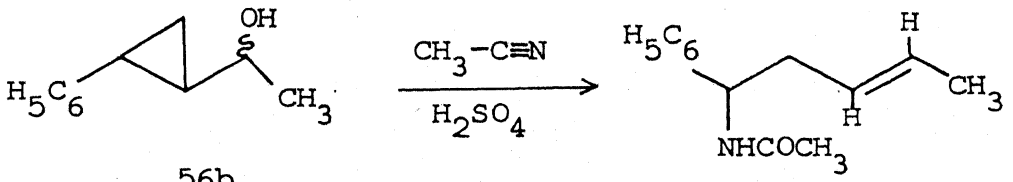
IR spectrum ν_{max}(KBr): 3325 (NH), 1655 (C=O-NH), 1630 (C=C), 1610 (C=C) cm^{-1}.

^{1}H NMR spectrum ($CDCl_3$ + DMSO D_6): 2.66 (t, 2H, J=7 Hz, allylic CH_2), 4.84–5.2 (m, 1H, C<u>H</u>–NH), 5.48 (dd, 1H, J=9 Hz, 4.5 Hz, COC<u>H</u>), 5.76–6.48 (m, 4H, CH=C<u>H</u>$_2$, and olefinic, J=15 Hz), 6.8–7.54 (m, 10H, aromatic), 8.36 (br, 1H, NH).

Mass spectrum, m/e (rel.int.): 277 (7, M^+), 276 (28), 222 (35, M^+–$COCH{=}CH_2$), 206 (42, M^+–$NH_2COCH{=}CH_2$), 160 (85), 106 (100).

Anal. Calcd for $C_{19}H_{19}NO$: C, 82.31; H, 6.86; N, 5.05. Found: C, 82.64; H, 6.88; N, 5.18.

Preparation of trans 1-N (acetyl)amino-1-phenylpent-3-ene (<u>59b</u>)



<u>56b</u> <u>59b</u>

The reaction of carbinol <u>56b</u> (100 mg, 0.62 mmol) with acetonitrile gave the amide <u>59b</u> which was purified by preparative thin layer chromatography [eluent, benzene:acetone (80:20)]. Yield, 85 mg (67%).

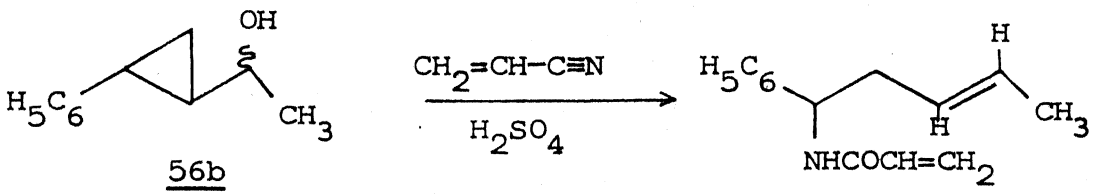
IR spectrum ν_{max} ($CHCl_3$): 3330 (NH), 1670 (C=O), 1610 (C=C) cm^{-1}.

^{1}H NMR spectrum ($CDCl_3$): δ 1.56 (d, 3H, J=6 Hz, CH_3), 1.92 (s, 3H, $COCH_3$), 2.4 (t, 2H, J=7 Hz, allylic CH_2), 4.8–5.15 (m, 1H, C<u>H</u>–NH), 5.25–5.9 (m, 2H, olefinic), 6.15–6.75 (br, 1H, NH), 7.3 (m, 5H, aromatic).

Mass spectrum, m/e (rel.int.): 203 (10, M^+), 160 (9, M^+-COCH_3), 145 (5, $M^+-NHCOCH_3$), 148 (55), 106 (100).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.85; H, 8.37; N, 6.89. Found: C, 76.64; H, 8.42; N, 6.95.

Preparation of trans-1-N(acrylyl)amino-1-phenylpent-3-ene (60b)



56b 60b

The reaction of carbinol 56b (100 mg, 0.62 mmol) with acrylonitrile gave the amide 60b which was purified by preparative thin layer chromatography [eluent, benzene-acetone (90:10)]. Yield, 80 mg (68%), m.p. 65-67°C.

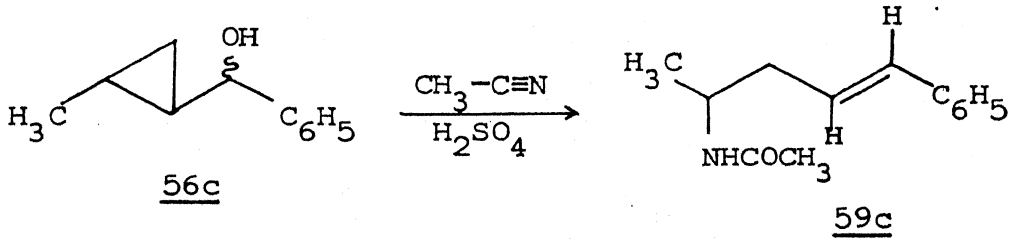
IR spectrum ν_{max}(KBr): 3330 (NH), 1655 (C=O), 1625 (C=C), 1610 (C=C) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.6 (d, 3H, J=6 Hz, CH_3), 2.5 (t, 2H, J=7 Hz, allylic CH_2), 4.96-5.25 (m, 1H, C<u>H</u>-NH), 5.33-5.7 (m, 3H, olefinic and COC<u>H</u>), 6.2 (m, 2H, CH=C<u>H</u>$_2$), 6.5-6.95 (br, 1H, NH), 7.3 (s, 5H, aromatic).

Mass spectrum, m/e (rel.int.): 215 (6, M^+), 160 (70, $M^+-COCH=CH_2$), 106 (100), 55 (65, $O=\overset{+}{C}-CH=CH_2$).

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.14; H, 7.91; N, 6.51. Found: C, 78.04; H, 8.02; N, 6.62.

Preparation of trans-2-N(acetyl)amino-5-phenylpent-4-ene (59c)



56c 59c

The reaction of 56c (100 mg, 0.62 mmol) with acetonitrile in the presence of conc. H_2SO_4 gave 59c. It was purified by preparative thin layer chromatography [eluent, benzene:acetone (80:20)]. Yield, 65 mg (51%).

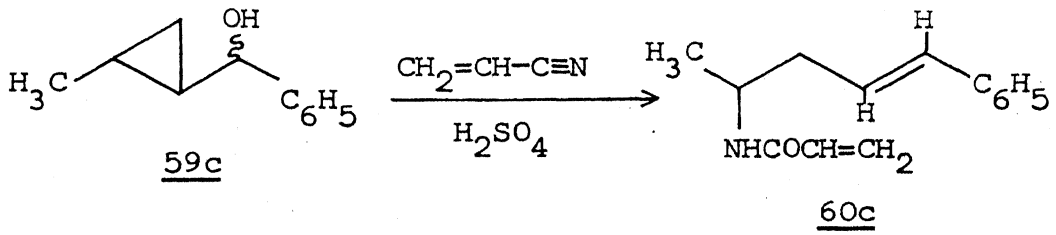
IR spectrum $\nu_{max}(CHCl_3)$: 3350 (NH), 1650 (C(=O)-NH) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.15 (d, 3H, J=7.5 Hz, CH_3), 1.9 (s, 3H, $COCH_3$), 3.38 (t, 2H, J=6 Hz, allylic CH_2), 3.9-4.33 (m, 1H, CH-NH), 5.55-5.95 (br, 1H, NH), 6.0-6.7 (m, 2H, olefinic, J=16.5 Hz), 7.32 (m, 5H, aromatic).

Mass spectrum, m/e (rel.int.): 203 (36, M^+), 160 (22, M^+-COCH_3), 145 (48, $M^+-NHCOCH_3$).

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.85; H, 8.37; N, 6.89. Found: C, 76.74; H, 8.35; N, 6.92.

Preparation of trans-2-N(acrylyl)amino-5-phenylpent-4-ene (60c)



59c 60c

The reaction of carbinol 56c (100 mg, 0.62 mmol) with acrylonitrile gave the amide 60c. The crude amide was purified by preparative thin layer chromatography [eluent, benzene:acetone (90:10)]. Yield, 60 mg (45%).

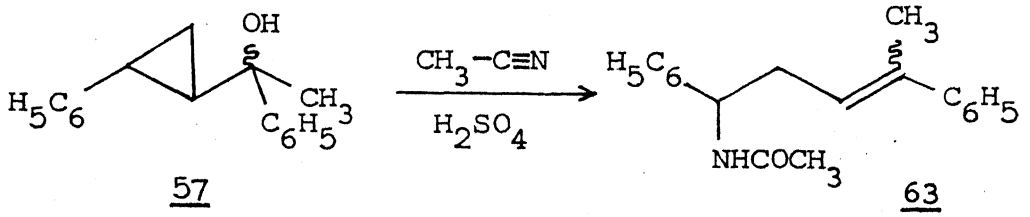
IR spectrum $\nu_{max}(CHCl_3)$: 3460 (NH), 1660 (C=O), 1630 (C=C), 1610 (C=C) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.15 (d, J=7.5 Hz, 3H, CH_3), 1.8 (br, 1H, NH), 2.36 (t, 2H, J=6 Hz, allylic CH_2), 4.0-4.5 (m, 1H, C<u>H</u>-NH), 5.4-6.5 (m, 5H, olefinic, J=15 Hz and COC<u>H</u>=C<u>H</u>$_2$), 7.28 (m, 5H aromatic).

Mass spectrum, m/e (rel.int.): 215 (15, M^+), 144 (40, M^+-$NH_2COCH=CH_2$), 118 (100), 117 (90).

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.14; H, 7.91; N, 6.51. Found: C, 78.05; H, 8.02; N, 6.39.

Preparation of 1-N(acetyl)amino-1,4-diphenylpent-3-ene (63)



57 63

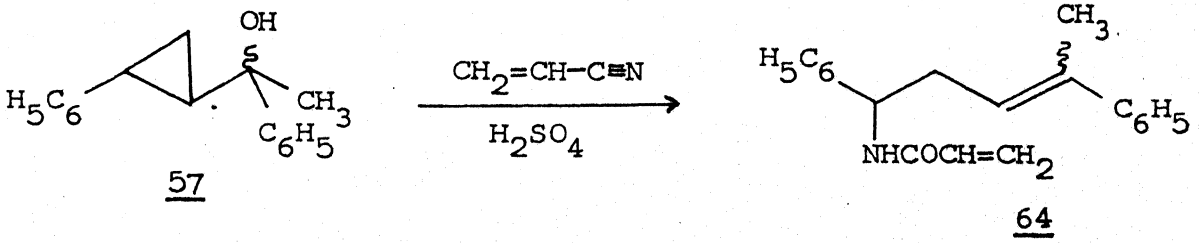
The reaction of carbinol 57 (100 mg, 0.42 mmol) with acetonitrile in the presence of conc. H_2SO_4 gave the amide 63 which was purified by preparative thin layer chromatography to obtain a thick oil [eluent, benzene:acetone (80:20)]. Yield, 70 mg (47%).

IR spectrum $\nu_{max}(CHCl_3)$: 3410 (NH), 1650 (C(=O)–NH) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 2.0 (s, 6H, CH_3 and $COCH_3$), 2.75 (t, 2H, J=7.5 Hz, allylic CH_2), 4.4–5.35 (br, 1H, NH), 5.18 (m, 1H, CH–NH), 5.55–6.1 (m, 1H, vinylic), 7.3 and 7.35 (2s, 10H, aromatic).

Anal. Calcd for $C_{19}H_{21}NO$: C, 81.72; H, 7.53; N, 5.02. Found: C, 81.80; H, 7.49; N, 5.18.

Preparation of 1-N(acrylyl)amino-1,4-diphenylpent-3-ene (64)



57 64

The reaction of the carbinol 57 (100 mg, 0.42 mmol) with

acrylonitrile in the presence of conc. H_2SO_4 gave the amide 64 which was purified by preparative thin layer chromatography [eluent, benzene:acetone (95:5)] to obtain a thick liquid. Yield 45 mg (37%).

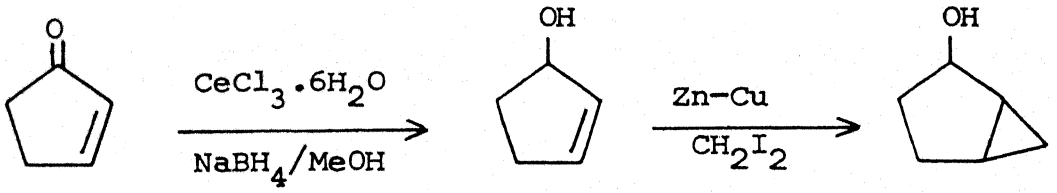
IR spectrum ν_{max}($CHCl_3$: 3410 (NH), 1650 (C(=O)–NH) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 2.0 (br, s, 3H, CH_3), 2.75 (t, 2H, J=7.5 Hz, allylic CH_2), 3.5–4.4 (br, 1H, NH), 5.2 (m, 1H, CH–NH), 5.55–6.3 (m, 4H, olefinic and $COCH=CH_2$), 7.28 and 7.33 (2s, 10H, aromatic).

Mass spectrum, m/e (rel.int.): 220 (40, $M^+-NH_2COCH=CH_2$), 160 (75), 106 (100).

Anal. Calcd for $C_{20}H_{21}NO$: C, 82.47; H, 7.22; N, 4.81. Found: C, 82.13; H, 7.28; N, 4.67.

Preparation of cis-bicyclo(3.1.0)hexan-2-ol (58a)



76a 58a

To a mixture of cyclopentenone (820 mg, 10 mmol) and $CeCl_3.6H_2O$ (3.55 g, 10 mmol) dissolved in methanol (25 mL), $NaBH_4$ (380 mg, 10 mmol) was added portionwise with stirring at room temperature. A vigorous gas evolution occured together with a temperature rise.

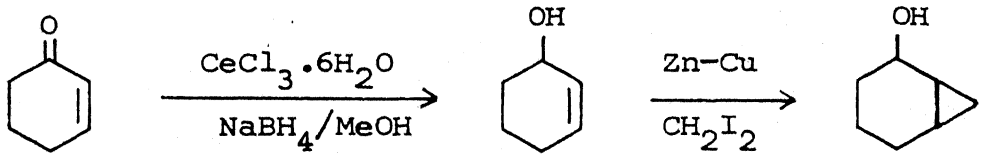
Stirring was continued for another 5 min and methanol was removed under reduced pressure. The residue was dissolved in ether (25 mL), neutralized with satd. aq. NH_4Cl and extracted with ether. The combined organic layer was washed with brine (10 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent followed by distillation gave the alcohol 76a.[44a] Yield 800 mg (95%), b.p. 58–60°C/25 mm (lit[44b], b.p. 65°C/35 mm).

A mixture of Zn–Cu couple (690 mg, 10.5 mmol), iodine (50 mg) and CH_2I_2 (0.8 mL, 14 mmol) in ether (20 mL) was refluxed gently for 30 min. 2-Cyclopentenol 76a (370 mg, 4.4 mmol) in ether (2 mL) was added during 30 min and the resulting mixture was refluxed for additional 1 h. After cooling it to room temperature satd. aq. NH_4Cl (5 mL) solution was added and the precipitated inorganic salts were washed with ether. The combined ethereal layer washed with satd. aq. K_2CO_3 (2 x 15 mL), satd. aq. NaCl (2 x 15 mL) and dried over anhydrous sodium sulphate. After removal of the ether, the residue was added to 3 mL of satd. solution of sodium methoxide in methanol and the mixture was allowed to stand overnight. Then, it was dissolved in ether (50 mL) and washed with brine until the aqueous washing (5 x 15 mL) was neutral to pH paper. The ethereal solution was dried over anhydrous sodium sulphate and the evaporation of ether gave a crude product which was purified by distillation. Yield, 275 mg (58%), b.p. 80–85°C/20 mm (lit[38], b.p. 78.0–79.5°C/20 mm).

IR spectrum $\nu_{max}(CHCl_3)$: 3400 (OH) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 0.5 (m, 2H, cyclopropyl CH_2), 1.5 (m, 6H, CH_2 and cyclopropyl C<u>H</u>), 3.9 (s, 1H, OH), 4.4 (m, 1H, C<u>H</u>–OH).

Preparation of cis-bicyclo (4.1.0)heptan-2-ol (<u>58b</u>)



<u>76b</u> <u>58b</u>

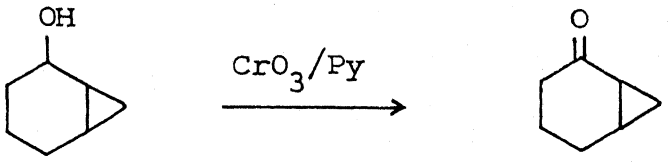
Following the above described procedure, the reaction of cyclohexenone (960 mg, 10 mmol), $CeCl_3.6H_2O$ (3.55 g, 10 mmol) and $NaBH_4$ (380 mg, 10 mmol) in methanol (25 mL) gave the alcohol <u>76b</u>. Yield, 950 mg (98%), b.p. 80–82°C/15 mm (lit[45], b.p. 61–62°C/11 mm).

The reaction of cyclohexenol (650 mg, 6.6 mmol) with Zn–Cu (1.17 g, 18 mmol) and CH_2I_2 (1.15 mL, 14 mmol) under reflux for 1 h gave the alcohol <u>58b</u> which was purified as described for <u>58a</u>. Yield, 425 mg (58%), b.p. 85–90°C/10 mm (lit[38], b.p. 76–77°C/10 mm).

IR spectrum ν_{max}(neat): 3400 (OH) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 0.2–0.7 (m, 2H, cyclopropyl CH_2), 0.85–2.0 (m, 8H, CH_2 and cyclopropyl C<u>H</u>), 3.7 (s, 1H, OH), 3.9–4.25 (m, 1H, C<u>H</u>–OH).

Preparation of bicyclo(4.1.0)heptan-2-one (50)



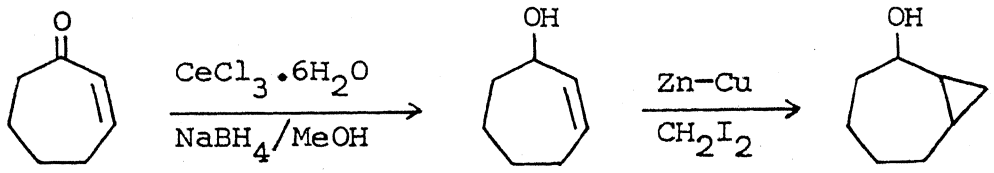
58b 50

To a stirred solution of distilled pyridine (1.44 mL, 17.8 mmol) in dry CH_2Cl_2 (15 mL) was added CrO_3 (892 mg, 8.92 mmol) portionwise at 15-20°C and the resultant mixture was allowed to stir for additional 30 min and celite (1 g) was added to it. The bicyclic alcohol 58b (100 mg, 0.892 mmol) in CH_2Cl_2 (0.5 mL) was added to the reagent in portion, then it was stirred for additional 30 min. The resultant mixture was diluted with anhydrous ether (50 mL), filtered through celite and washed thoroughly with plenty of ether (50 mL). The filtrate was evaporated to yield an oil which was purified by distillation. Yield, 55 mg (56%), b.p. 85-90°C/10 mm (lit[38], b.p. 85-85.5°C/10 mm).

IR spectrum ν_{max}(neat): 1680 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 0.85-1.32 (m, 2H, cyclopropyl CH_2), 1.5-2.7 (m, 8H, CH_2 and cyclopropyl CH).

Preparation of bicyclo(5.1.0)octan-2-ol (58c)



76c 58c

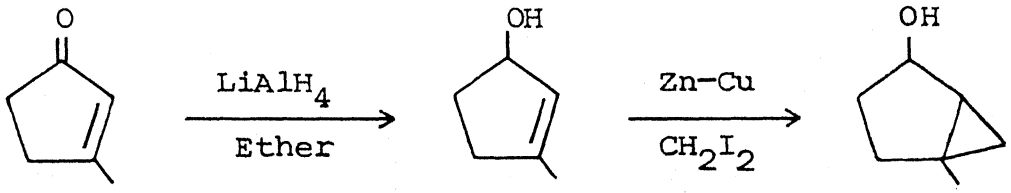
The reaction of 2-cycloheptenone (550 mg, 5 mmol) $CeCl_3.6H_2O$ (1.6 g, 5 mmol) and $NaBH_4$ (190 mg, 5 mmol) in methanol (12.5 mL) gave the alcohol 76c. Yield, 500 mg (90%), b.p. 80-83°C/20 mm (lit[38], b.p. 75-76°C/17 mm).

Following the above described procedure for 58a, the reaction of alcohol 76c (350 mg, 3.1 mmol), Zn-Cu (450 mg, 6.9 mmol) and CH_2I_2 (0.5 mL, 6.3 mmol) under reflux for 1h gave the alcohol 58c. Yield 290 mg (74%), b.p. 95-100°C/10 mm (lit[38], b.p. 90.5-91.5°C/10 mm).

IR spectrum ν_{max}(neat): 3350 (OH) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 0.45 (m, 2H, cyclopropyl CH_2), 0.65-2 (m, 10H, CH_2 and cyclopropyl CH), 2.25 (s, 1H, OH), 4.05-4.3 (m, 1H, CH-OH).

Preparation of cis-5-methyl bicyclo(3.1.0)hexan-2-ol (58d)



76d 58d

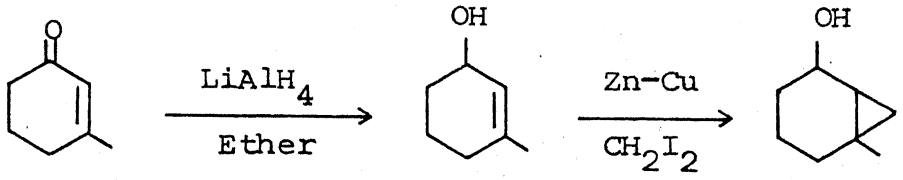
To a stirred solution of 3-methylcyclopenten-2-one (650 mg, 6.77 mmol) in ether (10 mL) at 10°C was added $LiAlH_4$ (1.30 mg, 3.4 mmol) portionwise and stirring continued for additional 2 h at room temperature. The reaction mixture was treated with satd. aq. NH_4Cl, solution, and the precipitated inorganic salts were washed with ether. The combinedetherlayer was washed with brine (10 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude product which was purified by distillation. Yield 450 mg (68%), b.p. 70-75°C/25 mm (lit[46], b.p. 77-78°C/30 mm).

The reaction of the alcohol 76d (700 mg, 7.14 mmol), CH_2I_2 (1.7 mL, 21 mmol) and Zn-Cu (1.7 g, 26 mmol) in ether under reflux for 6 h gave the alcohol 58d. Yield, 150 mg (20%), b.p. 65-70°C/ 10 mm (lit[47], b.p. 76°C/18 mm).

IR spectrum $\nu_{max}(CHCl_3)$: 3400 (OH) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 0.15-0.4 (m, 1H, cyclopropyl CH_2), 0.55-0.84 (m, 1H, cyclopropyl CH_2), 0.9-1.9 (m, 5H, CH_2 and cyclopropyl CH), 1.2 (s, 3H, CH_3), 2.0 (s, 1H, OH), 4.45-4.75 (m, 1H, C<u>H</u>-OH).

Preparation of cis-6-methyl bicyclo(4.1.0)heptan-2-ol (58e)



76e 58e

Following the above described procedure for 58d, the reaction of 3-methylcyclohexen-2-one (550 mg, 5 mmol) with $LiAlH_4$ (95 mg, 2.5 mmol) at room temperature for 30 min gave the alcohol 76e. Yield, 500 mg (89%), b.p. 80-83°C/10 mm (lit[45], b.p. 74-75°C/10 mm).

The reaction of alcohol 76e (1.0 g, 8.93 mmol) Zn-Cu (1.35 g, 20.6 mmol) and CH_2I_2 (1.53 mL, 19 mmol) in ether under reflux for 4 h gave the alcohol 58e. Yield, 900 mg (80%), b.p. 80-85°C/10 mm (lit[47], b.p. 74-75°C/10 mm).

IR spectrum ν_{max}(neat): 3350 (OH) cm^{-1}.

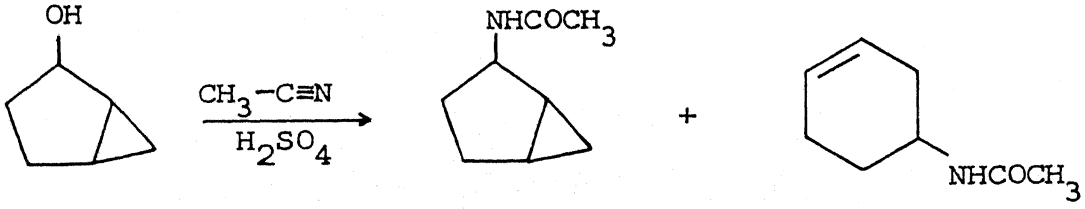
^1H NMR spectrum (CCl_4(: δ 0.1-0.65 (2m, 2H, cyclopropyl CH_2), 0.8-1.8 (m, 7H, CH_2 and cyclopropyl CH), 1.05 (s, 3H, CH_3), 1.9 (s, 1H, OH), 3.95-4.25 (m, 1H, C<u>H</u>-OH).

General procedure for the reaction of bicyclic alcohols with nitriles in the presence of conc. H_2SO_4

To 1.5 mmol of conc. H_2SO_4 at 0°C was introduced slowly 1.0 mL of nitrile and stirred for 30 min. A solution of 1 mmol of

carbinol in 1.0 mL of nitrile was then added slowly at $-10^{o}C$ during 15 min. After stirring for additional 10 min., 10 g of ice was added to the reaction mixture and neutralized with saturated solution $NaHCO_3$. The aqueous layer was saturated with NaCl and extracted with ethyl acetate (3 x 15 mL). It was washed with brine, dried over anhydrous sodium sulphate and evaporated to obtain a crude product which was further purified.

Preparation of 2-N(acetyl)bicyclo(3.1.0)hexylamine (65a) and N(acetyl)cyclohex-3-enylamine (66a)



58a 65a 66a

The reaction of 58a (100 mg, 1.02 mmol) with acetonitrile gave a mixture of amides 65a and 66a. Yield, 60 mg (43%).

IR spectrum $\nu_{max}(CHCl_3)$: 3440 (NH), 1660 (C=O-NH) cm^{-1}.

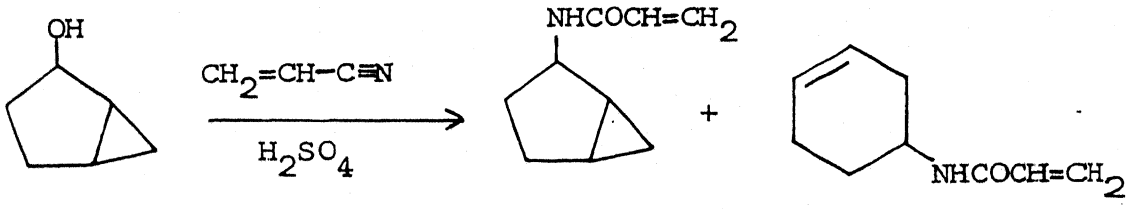
^1H NMR spectrum ($CDCl_3$): δ 0.31 (m, 2H, cyclopropyl CH_2), 0.62-2.56 (m, 6H, CH_2 and cyclopropyl CH), 3.15-3.65 (br, 1H, NH), 4.06 (m, 1H, CH-NH), 4.25 (m, 1H, CH-NH), 5.65 (m, 2H, olefinic).

Mass spectrum, m/e (rel.int.): 139 (10, M^+), 96 (16, M^+-COCH_3), 80 (44, $M^+-NH_2COCH_3$), 60 (100).

Gas chromatographic analysis: column SE-30, temp. 140°C, N_2 flow 50 mL/min. Retention time 9.16 min, 9.86 min., Ratio 50:50.

Anal. Calcd for $C_8H_{13}NO$: C, 69.06; H, 9.35; N, 10.07. Found: C, 69.12; H, 9.45; N, 9.93.

Preparation of 2-N(acrylyl)bicyclo(3.1.0)hexylamine (67a) and N (acrylyl)cyclohex-3-enylamine (68a)



58a 67a 68a

The reaction of 58a (100 mg, 1.02 mmol) with acrylonitrile gave a mixture of amides 67a and 68a. Yield, 45 mg (30%).

IR spectrum $\nu_{max}(CHCl_3)$: 3440 (NH), 1670 (C(=O)-NH), 1630 (C=C), 1610 (C=C) cm^{-1}.

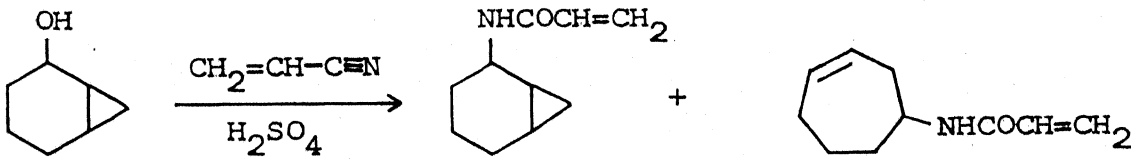
^1H NMR spectrum ($CDCl_3$): δ 0.36 (m, 2H, cyclopropyl CH_2), 0.7-2.68 (m, 6H, CH_2, cyclopropyl CH), 2.3-2.7 (br, 1H, NH), 4.28 (m, 1H, C<u>H</u>-NH), 4.59 (m, 1H, C<u>H</u>-NH), 5.5-5.75 (m, 3H, olefinic and COC<u>H</u>=CH_2), 6.05-6.3 (m, 2H, COCH=C<u>H</u>$_2$).

Mass spectrum, m/e (rel.int.): 151 (6, M^+), 96 (32, M^+-$COCH=CH_2$), 81 (42, M^+-$NHCOCH=CH_2$), 72 (100).

Gas chromatographic analysis: column SE-30, temp. 170°C N_2 flow 50 mL/min, Retention time 5.55 min., 6.0 min. Ratio 45:55.

Anal. Calcd for $C_9H_{15}NO$: C, 70.59; H, 9.80; N, 9.15. Found: C, 70.65; H, 9.70; N, 9.22.

Preparation of 2-N(acrylyl)bicyclo(4.1.0)heptylamine (67b) and N(acrylyl)cyclohept-3-enylamine (68b)



58b 67b 68b

Following the above described procedure, the reaction of carbinol 58b (100 mg, 0.892 mmol) with acrylonitrile gave a product which was a mixture of amides 67b and 68b. Yield, 70 mg (48%).

IR spectrum $\nu_{max}(CHCl_3)$: 3430 (NH), 1660 (C(=O)-NH), 1620 (C=C), 1610 (C=C) cm^{-1}.

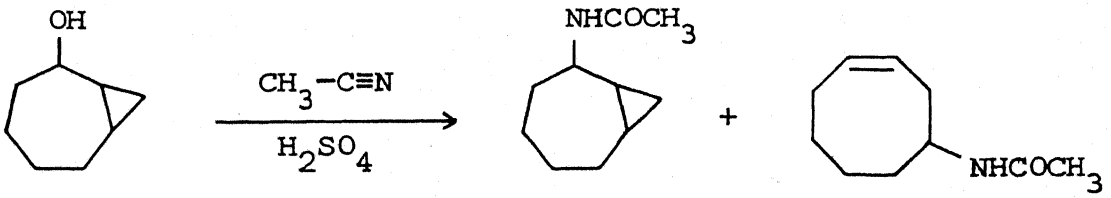
^1H NMR spectrum ($CDCl_3$): δ 0.4-2.47 (m, 10H, CH_2 and cyclopropyl CH_2), 3.5-3.85 (br, 1H, NH), 4.19 (m, 1H, C<u>H</u>-NH), 4.41 (m, 1H, C<u>H</u>-NH), 5.5-6.35 (m, 5H, olefinic and COC<u>H</u>=C<u>H</u>$_2$).

Mass spectrum, m/e (rel.int.): 165 (13, M^+), 110 (30, M^+-$COCH=CH_2$), 95 (27, M^+-$NHCOCH=CH_2$), 94 (100, M^+-$NH_2COCH=CH_2$), 55(98).

Gas chromatographic analysis: column SE-30, temp. 170°C, N_2 flow 50 mL/min., Retention time, 7.13 min., 7.75 min., Ratio 45:55.

Anal. Calcd for $C_{10}H_{15}NO$: C, 72.73; H, 5.09, N, 8.48. Found: C, 72.82; H, 8.85; N, 8.35.

Preparation of 2-N(acetyl)bicyclo(5.1.0)octylamine (65c) and N(acetyl)cyclooct-3-enylamine (66c)



58c 65c 66c

Following the above described procedure the reaction of 58c (100 mg, 0.79 mmol) gave a mixture of amides 65c and 66c. Yield, 100 mg (76%).

IR spectrum $\nu_{max}(CHCl_3)$: 3460 (NH), 1670 (C(=O)–NH) cm^{-1}.

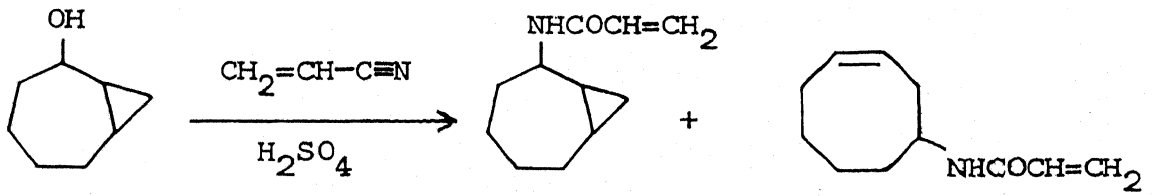
^1H NMR spectrum ($CDCl_3$): δ 0.36 (m, 1H, cyclopropyl CH_2), 0.55-2.5 (m, 11H, CH_2 and cyclopropyl CH), 2.05 (br, s,3H,$COCH_3$), 3.28-3.7 (m, 1H, CH–NH), 3.8-4.25 (m, 1H, CH–NH), 5.36-6.25 (m, 2H, olefinic), 6.45-7.1 (br, 1H, NH).

Mass spectrum, m/e (rel.int): 167 (11, M^+), 124 (17, M^+-COCH_3), 109 (10, $M^+-NHCOCH_3$), 108 (65, $M^+-NH_2COCH_3$), 56 (100).

Gas chromatographic analysis: column SE-30, temp. 170°C, N_2 flow 50 mL/min Retention time 7.24 min., 8.12 min, Ratio 50:50.

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.86; H, 10.18; N, 8.38. Found: C, 71.98; H, 10.10; N, 8.46.

Preparation of 2-N(acrylyl)bicyclo(5.1.0)octylamine (67c) and N(acrylyl)bicyclo(5.1.0)oct-3-enylamine (68c)



58c 67c 68c

The alcohol 58c (100 mg, 0.79 mmol) with acrylonitrile gave a mixture of amides 67c and 68c. Yield, 105 mg (74%).

IR spectrum $\nu_{max}(CHCl_3)$: 3460 (NH), 1670 (C(=O)-NH), 1620 (C=C) cm^{-1}.

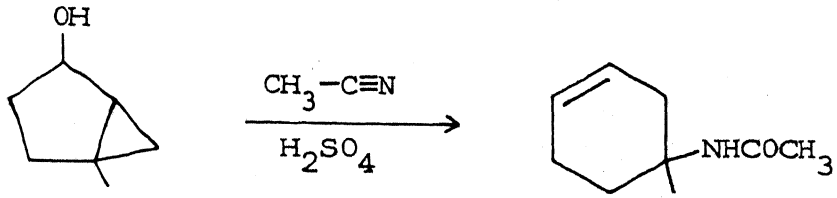
^1H NMR spectrum ($CDCl_3$): δ 0.15-2.6 (m, 12H, cyclopropyl CH_2 and CH_2), 3.3-4.33 (br, 2H, C<u>H</u>-NH and NH), 5.5-6.36 (m, 5H, olefinic and CO<u>CH</u>=<u>CH$_2$</u>).

Mass spectrum, m/e (rel.int.): 179 (7, M^+), 124 (18, M^+-$COCH=CH_2$), 109 (15, M^+-$NHCOCH=CH_2$), 108 (55, M^+-$NH_2COCH=CH_2$).

Gas chromatographic analysis: column SE-30, temp. 170°C N_2 flow 50 mL/min Retention time 7.52 min and 8.44 min, Ratio 50:50.

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.74; H, 9.50; N, 7.82. Found: C, 73.82; H, 9.60; N, 7.75.

Preparation of 1-methyl-N(acetyl)cyclohex-3-enylamine (66d)



58d 66d

The reaction of the alcohol 58d (100 mg, 0.892 mmol) with acetonitrile gave a crude product which was purified by preparative thin layer chromatography [eluent, benzene:acetone (80:20)]. Yield 80 mg (78%).

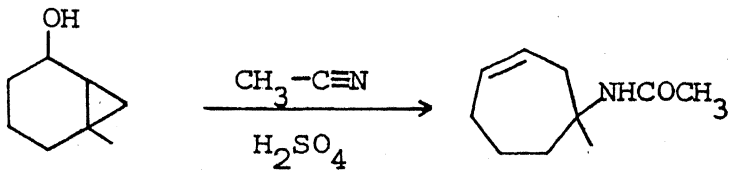
IR spectrum $\nu_{max}(CHCl_3)$: 3440 (NH), 1665 (C=O–NH) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.4 (s, 3H, CH_3), 1.98 (s, 3H, $COCH_3$), 1.8-2.5 (m, 6H, CH_2), 5.35-6.0 (m, 2H, olefinic), 7.5-7.9 (br, 1H, NH).

Mass spectrum, m/e (rel. int.): 153 (5, M^+), 110 (6, M^+-COCH_3), 95 (14, $M^+-NHCOCH_3$), 94 (96, $M^+-NH_2COCH_3$), 60 (100).

Anal. Calcd for $C_9H_{15}NO$: C, 70.59; H, 9.80; N, 9.15. Found: C, 70.63; H, 9.72; N, 9.10.

Preparation of 1-methyl-N(acetyl)cyclohept-3-enylamine (66e)



58e 66e

The reaction of the alcohol 58e (100 mg, 0.79 mmol) with acetonitrile at -40°C for 1 h gave the amide 66e which was purified by preparative thin layer chromatography [eluent, benzene:acetone (80:20)]. Yield 24 mg (18%).

IR spectrum $\nu_{max}(CHCl_3)$: 3440 (NH), 1670 ($\overset{O}{\overset{\|}{C}}$-NH) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.43 (s, 3H, CH_3), 1.93 (s, 3H, $COCh_3$), 1.2-2.5 (m, 8H, CH_2), 4.1-4.6 (br, 1H, NH), 5.4-6.2 (m, 2H, olefinic).

Mass spectrum, m/e (rel.int.): 167 (13, M^+), 124 (10, $M^+ - COCH_3$), 109 (7, $M^+-NHCOCH_3$), 108 (70, $M^+-NH_2COCH_3$), 70 (100).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.86; H, 10.18; N, 8.38. Found: C, 71.62; H, 10.26; N, 8.20.

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CHAPTER - III

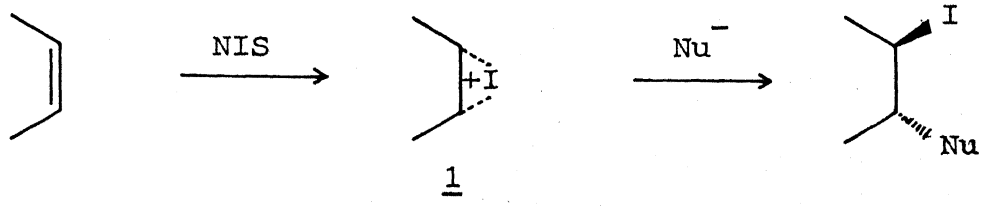
PART - A

DEVELOPMENT OF SYNTHETIC METHODS BASED ON SODIUM IODIDE-N-CHLOROSUCCINIMIDE AND SODIUM IODIDE-CHLOROTRIMETHYLSILANE REAGENT SYSTEMS

(i) Synthesis of N-iodosuccinimide from N-chlorosuccinimide and sodium iodide and its utility in the synthesis of α-iodocarbonyl compounds.

III.A.(i) 1. Introduction

N-Iodosuccinimide (NIS) has been found to be a convenient source for iodonium ion, I^+. This reagent has been utilized for various synthetic transformations in organic chemistry. In steroid chemistry[1] it has been used for the synthesis of α-iodocarbonyl compounds starting from enol acetates. NIS has been found to form iodonium ion intermediate 1 with olefin which interacts with nucleophiles (other than succinimide anion) to produce trans iodo compounds. Various nucleophiles have been reported in the literature[2] for this purpose. For example,



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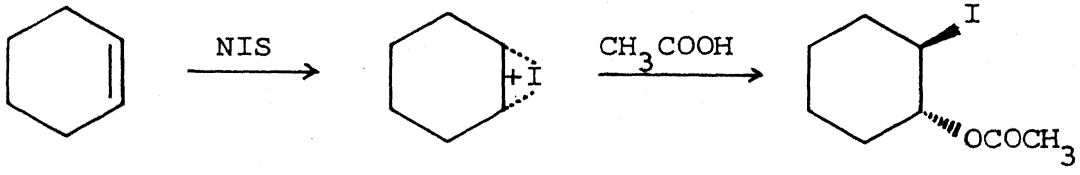
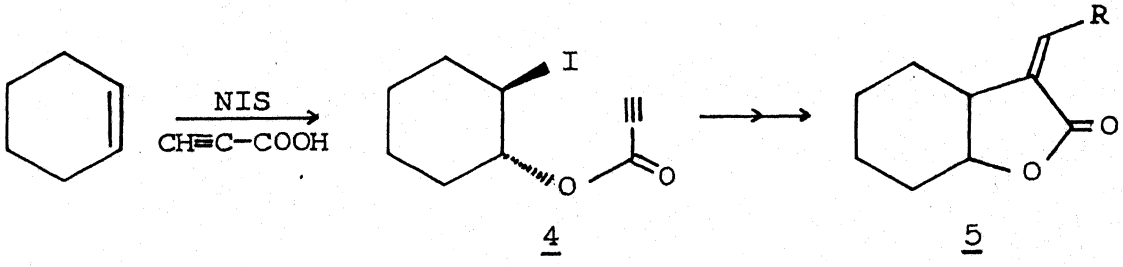
carboxylic acids have been shown to add readily to this intermediate. Reaction of cyclohexene with CH_3COOH in the presence of



2 3

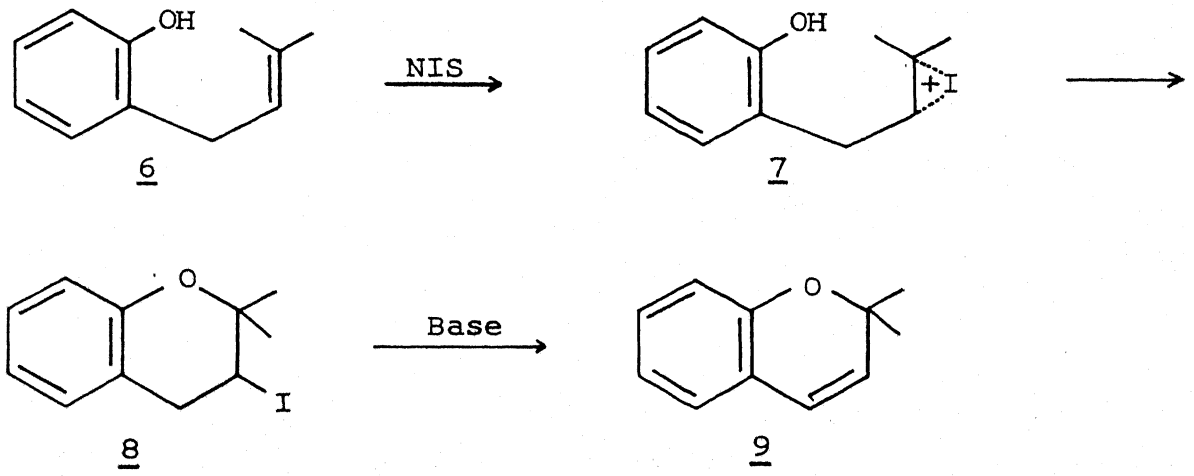
NIS gave trans-1,2-iodoacetate[3] 3. Recently[4] propargylic acid has been reacted with this intermediate to give 4 which has been further converted into α-methylene butyrolactone 5 using radical chemistry (Scheme III.A.1).



4 5

Scheme III.A.1

Alcohols and phenols have also been utilized as nucleophiles for this purpose. Chromenes and Flavenes have been synthesized following such reaction.[5] Thus, for example, reaction of 6 with NIS gave 8 which was then converted to the Chromene 9 (Scheme III.A.2). In the above reaction, usual conditions, reported for



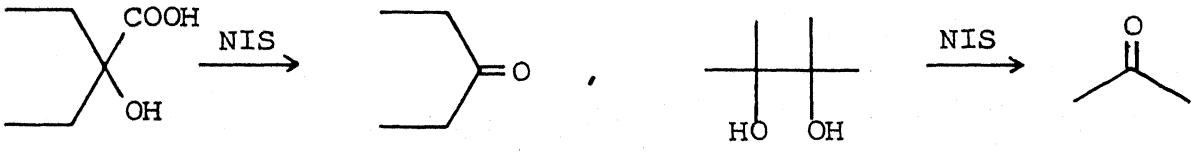
Scheme III.A.2

the iodolactonization have been found to promote the aromatic ring iodination. However, with NIS no such problem is encountered and thus, it has been shown to be a successful reagent for the above reaction.

Stereoselective synthesis of glycosides has been one of the current interest in synthetic organic chemistry as a result of isolation and structure elucidation of a number of biologically important glycosidic compounds. NIS has been found to be one of the best reagent for the stereoselective synthesis of glycosides.[6] Thus, for example, intermolecular reaction[6a] of 10 and 11 in the presence

of NIS gave exclusively α-isomer 12 (Scheme III.A.3). On the other hand intramolecular cyclization[6b] of 13 in the presence of NIS gave a mixture of α and β isomers 14 and 15 in the ratio 120:1 similarly 16 gave 17 and 18 in the ratio 7:3 (Scheme III.A.4).

NIS has also been used as an oxidizing agent. Beebe et al.[7] have extensively studied the oxidation of primary, secondary and tertiary alcohols.[7a] They have also shown the utility of this reagent for the oxidative decarboxylation of hydroxy acids[7b] and for the cleavage of diols to aldehydes or ketones[7c] (Scheme III.A.5).

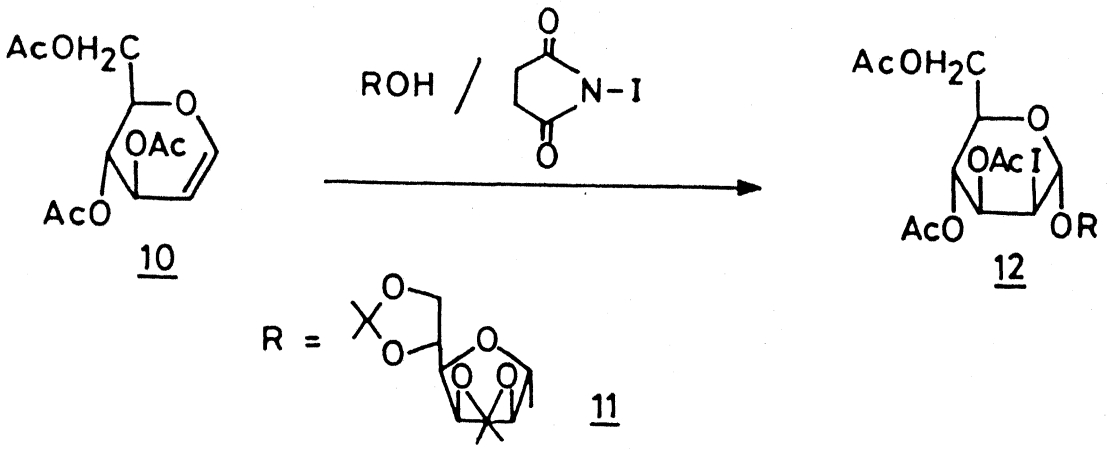


Scheme III.A.5

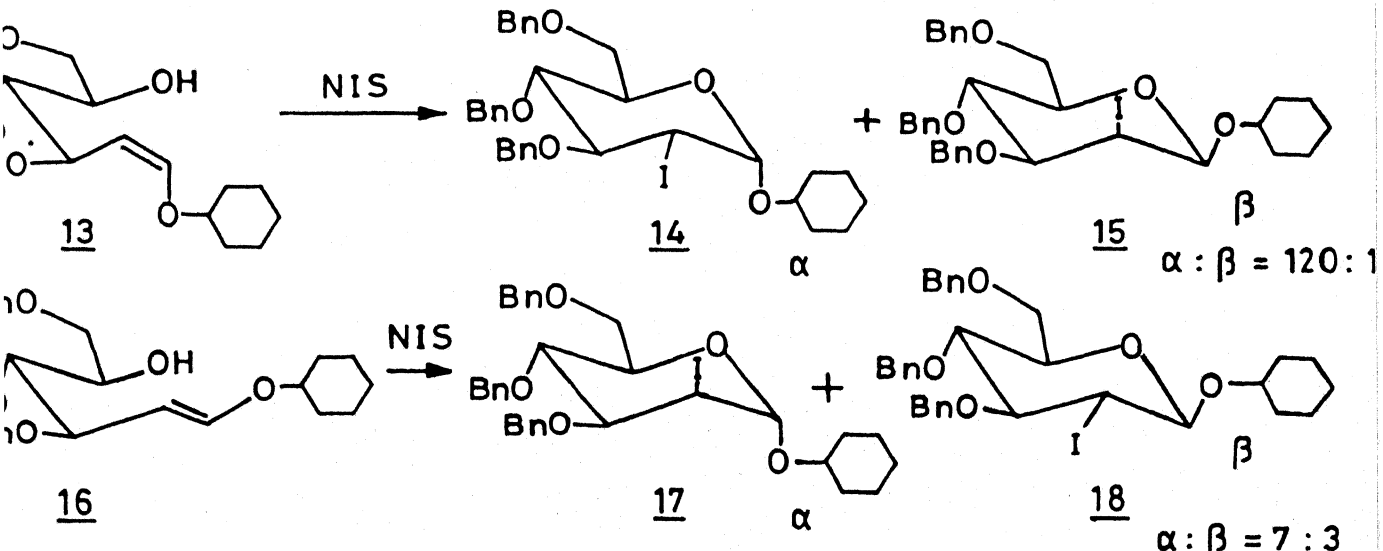
The above reactions were found to proceed via alkyl hypoiodite.

NIS has been utilized for the selective hydrolysis of dithiane in the synthesis of Vermiculin .[8] Thus 19, an intermediate in Vermiculin synthesis was hydrolyzed selectively to give 20 using NIS (Scheme III.A.6).

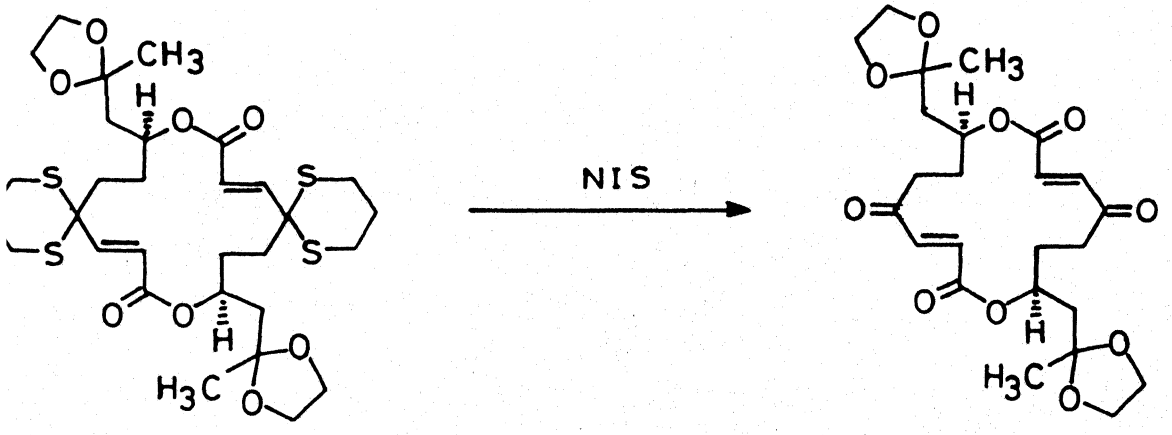
In contrast to their chloro and bromo analogs, α-iodocarbonyl compounds have been studied infrequently. This is primarily due to the relative instability of such compounds and also due to the fact



Scheme III.A.3

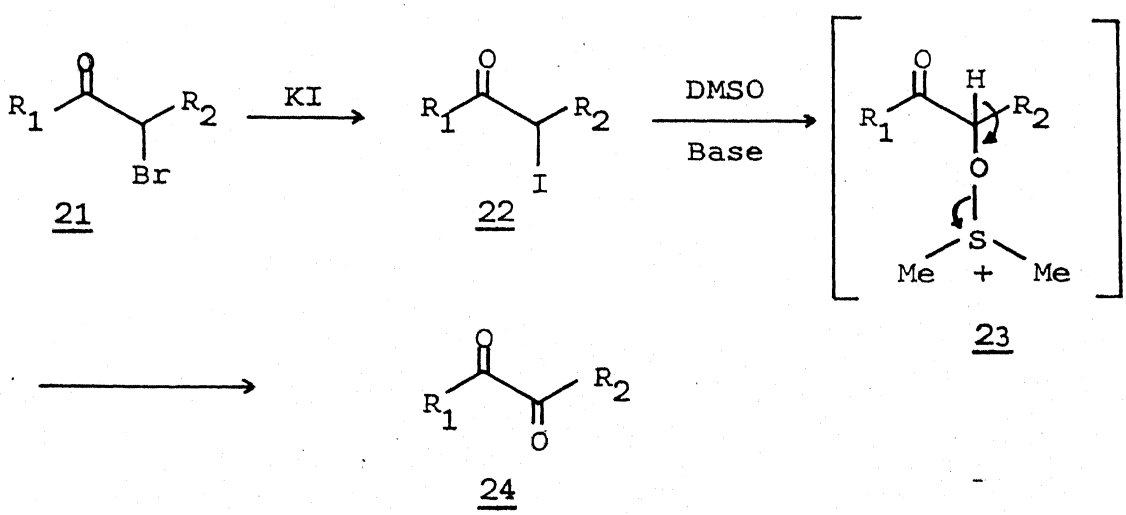


Scheme III.A.4



Scheme III.A.6

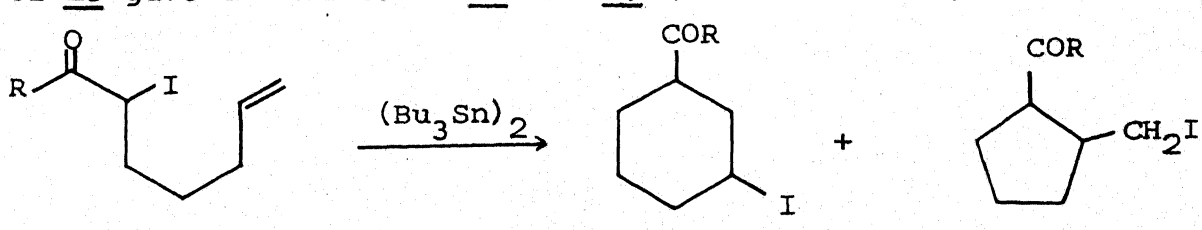
that methods available for their synthesis are limited. α-Iodocarbonyl compounds have been shown to be important intermediates in the synthesis of 1,2-diketones.[9] For example, α-bromoketone 21 was reacted with KI in DMSO followed by treatment with base to give 1,2-diketone 24. This reaction has been proposed to proceed via α-iodoketone 22 (Scheme III.A.7).



21 22 23 24

Scheme III.A.7

Recently[10] α-iodocarbonyl compounds have been shown to be radical precursors. For example, intramolecular radical cyclization of 25 gave a mixture of 26 and 27 (Scheme III.A.8).



25 26 27

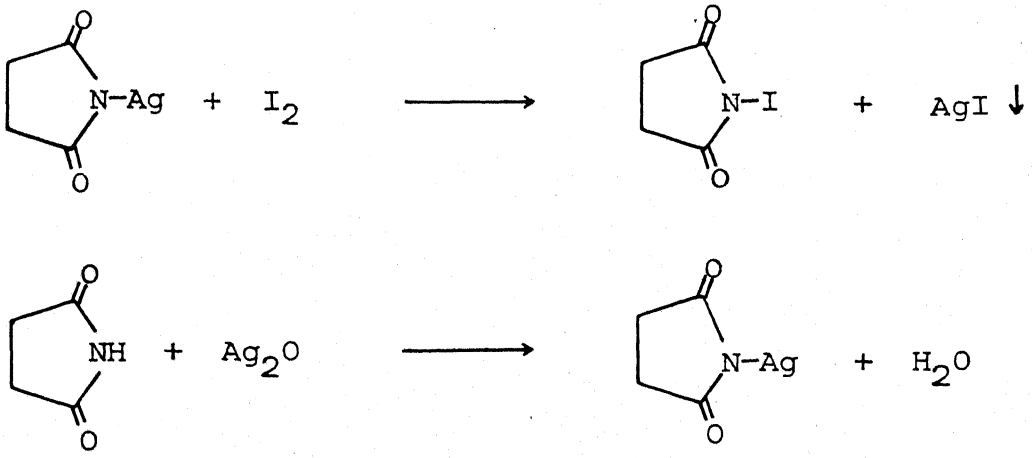
Scheme III.A.8

α-Iodoketones have previously been prepared by halogen interchange[11] of α-bromocarbonyl compounds with sodium iodide and by the reaction of NIS or iodine monochloride with enol acetates of ketones.[1,12] Thallium acetate - iodine[13] and silver acetate-iodine[14] have also been used as reagents for the preparation of α-iodoketones from enol acetates and enol silyl ethers respectively. But these methods involve the use of either highly toxic thallium acetate or the expensive silver acetate. However, Piancatelli et al.[15] have reported a fairly simple synthesis of α-iodocarbonyl compounds starting from enol silyl ethers using pyridinium chlorochromate-iodine combination. Other recently developed methods of converting ketones into α-iodocarbonyl compounds using $HgCl_2$-iodine[16a] and ceric ammonium nitrate-iodine[16b] have not been found to be regiospecific.

In addition to these, there are few reports in the literature for the direct conversion of alkenes to the corresponding α-iodoketones. For example, silver chromate-iodine has been used earlier for this purpose.[17] Recent methods for the preparation of α-iodoketones include the use of pyridinium dichromate-iodine[18] and bis(sym-collidine)iodine(I) tetrafluoroborate-DMSO.[19]

III.A(i).2 Results and Discussion

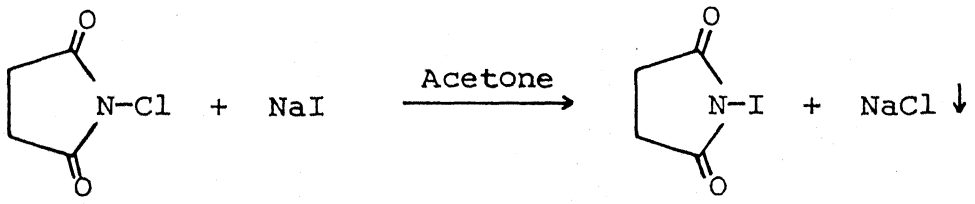
In the introduction part of this chapter, the importance of NIS in organic synthesis has been described. To our knowledge, only one method is available in the literature[20] for the preparation of NIS. This method involves the reaction of silver succinimide and iodine where silver succinimide was prepared from succinimide and silver oxide (Scheme III.A.9). This method of preparation of NIS is an expensive one because of the use of silver oxide.



Scheme III.A.9

Hence, an alternate procedure for its preparation is needed. Furthermore, NIS has been found to be unstable towards light and heat. It is therefore highly desirable that an easy method is developed to prepare it, so that it could be used as and when required. We sought a newer, cheaper and convenient approach of its preparation.

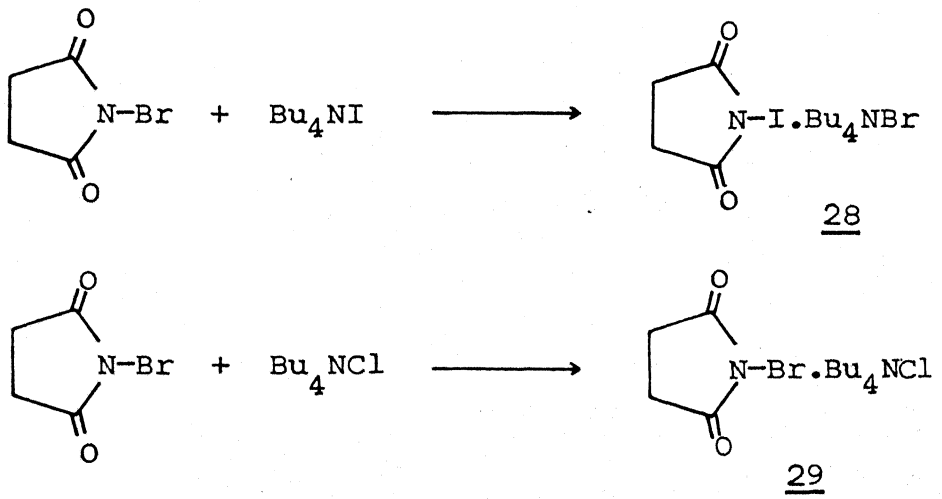
Interestingly, N-chlorosuccinimide (NCS), unlike NIS, is cheap and stable towards heat and light. If there is an easy way of exchanging the chlorine with iodine, NIS could be readily prepared. It was indeed found to be the case.Thus, treatment of NCS with sodium iodide in acetone was found to give NIS and sodium chloride precipitate out. Filtration of NaCl and evaporation of the solvent gave essentially pure NIS in 95% yield. Analytical sample was prepared by recrystallizing the crude product from



dioxan-CCl_4 mixture and the melting point was compared with the authentic sample. The present methodology for its preparation is more convenient and cheaper compared to the one reported in the literature.[20] Present method avoids the use of expensive silver salts and it could be prepared conveniently whenever it is needed. It has also been found (vide infra) that it could be generated in situ and used without filtering sodium chloride wherever Cl^- does not interfere the reactions.

It is obvious that there is a direct halogen exchange between NCS and sodium iodide. More recently, after our publication,[21] a report appeared in the literature[22] where a combination of N-halosuccinimide and quaternary ammonium halide was found to give a 1:1

or 1:2 complex. For example, N-bromosuccinimide (NBS) and tetrabutylammonium iodide in acetone-ether gave a 1:1 complex 28 with halogen interchange. On the other hand the reaction of NBS with tetrabutylammonium chloride gave a complex 29 without halogen interchange (Scheme III.A.10).

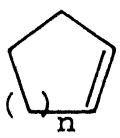


Scheme III.A.10

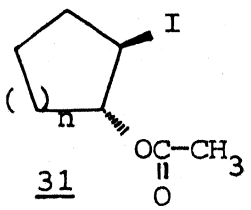
In order to test the applicability of this reagent, a known reaction was carried out and the results were compared with the reactions done with commercially available NIS. Thus, the reaction of cyclohexene with NIS (prepared from NCS and sodium iodine) in $CHCl_3$ in the presence of acetic acid gave trans-1,2-iodoacetate 31b, as reported in the literature[3] with commercially available NIS, in 92% yield. The same reaction was carried out with commercially available NIS also where the product was obtained in 95% yield. Spectral properties of the product obtained from NCS-NaI reaction were similar to that obtained using commercial NIS.

Similarly various olefins 30a-d and 32 were reacted with both NCS-NaI and commercially available NIS and the yields are shown in Table III.A.1 for comparison. Reaction of 32 with NCS-NaI or with NIS was found to give a mixture of two products 33 and 34 in the ratio 30:70 which was determined on the basis of ^{1}H NMR spectrum.

Table III.A.1

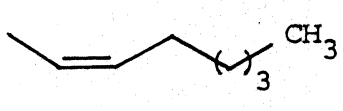


30

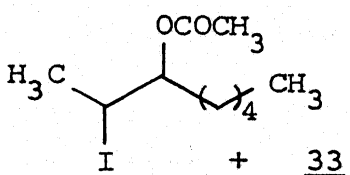


31

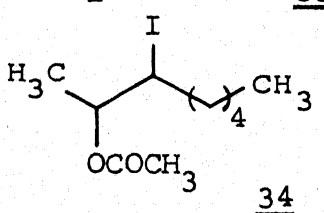
		% Yield using	
		NCS-NaI	NIS
a	n = 1	92	95
b	n = 2	92	97
c	n = 3	89	95
d	n = 8	88	89



32



33 +

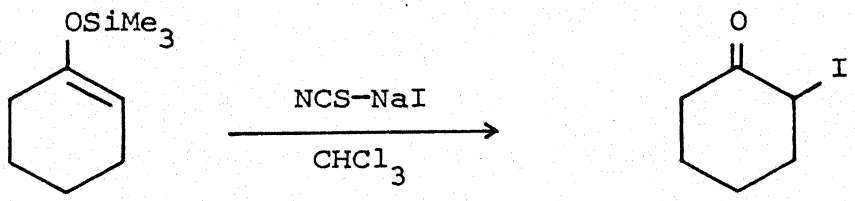


34

77	80	

In the above mentioned reactions, crude NIS obtained, from a mixture of NCS and sodium iodide in acetone after filtration of NaCl, was used as such without further purification. Filtration of sodium chloride was necessary because the chloride ion present in the medium may compete with carboxylic acid to react with the iodinium ion intermediate. However, we have successfully used the in situ generated NIS, from NCS and NaI, in its application to the synthesis of α-iodocarbonyl compounds from enol silyl ethers without the filtration of sodium chloride.

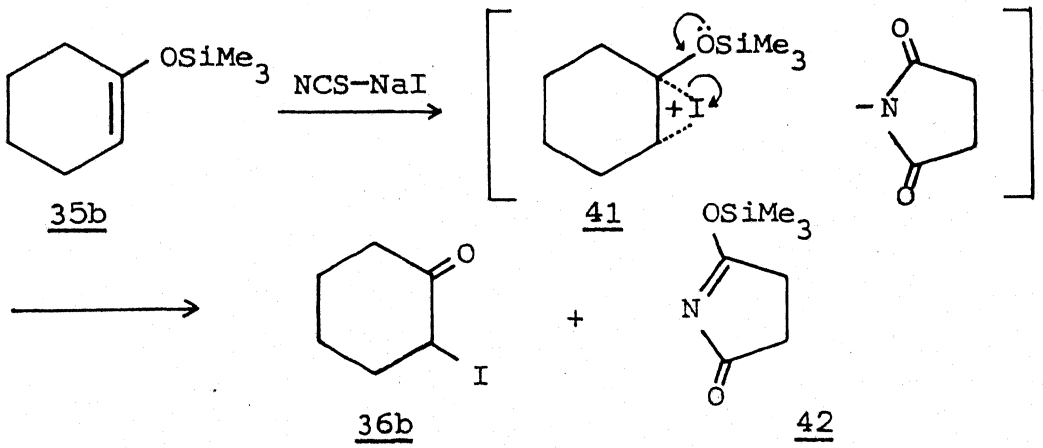
Importance of α-iodocarbonyl compounds and their methods of preparation were presented in the introduction part of this chapter. Methods reported in the literature have been found to involve either toxic or expensive reagents and thus more methods to prepare α-iodocarbonyl compounds are necessary to be developed. This promted us to use NIS, generated from NCS and NaI, for the preparation of α-iodocarbonyl compounds from enol silyl ethers, easily obtainable starting materials. Thus, the reaction of enol silyl ether 35b with NCS and NaI in $CHCl_3$ at 0°C for 30 min gave α-iodocyclohexanone (36b) in 83 % yield. IR spectrum of 36b showed



35b 36b

absorptions at δ 1.50–2.35 (m, 7H, CH_2), 3.25 (m, 1H, C<u>H</u>–C(I)), 4.73 (m, 1H, C<u>H</u>–I). Further, its mass spectrum indicated a molecular ion peak at 224 and a base peak at 97 (M^+–I). These data are comparable with the literature[19] values of the compound <u>36b</u>.

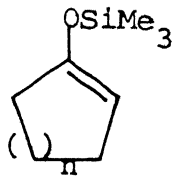
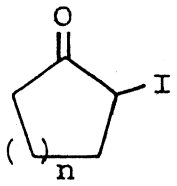
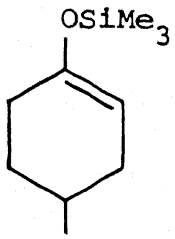
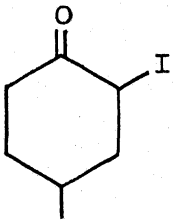
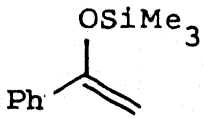
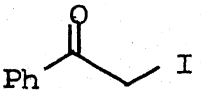
A plausible mechanism for the formation of the product is shown in Scheme III.A.11. The reaction may be considered to proceed via the intermediate <u>41</u> which decomposed to produce α-iodoketone and water soluble succinimide <u>42</u>.



Scheme III.A.11

Synthesis of α-iodoketones from enol silyl ether was also carried out with commercially available NIS and the yields were found to be comparable with those obtained using NCS–NaI mixture. Various enol silyl ethers <u>35a–c</u>, <u>37</u> and <u>39</u> were used for its purpose and the results are shown in Table III.A.2.

Table III.A.2

			% Yield using	
	 35	 36	NCS-NaI	NIS
a	n = 1		76	76
b	n = 2		83	84
c	n = 3		85	86
			74	74
			71	72

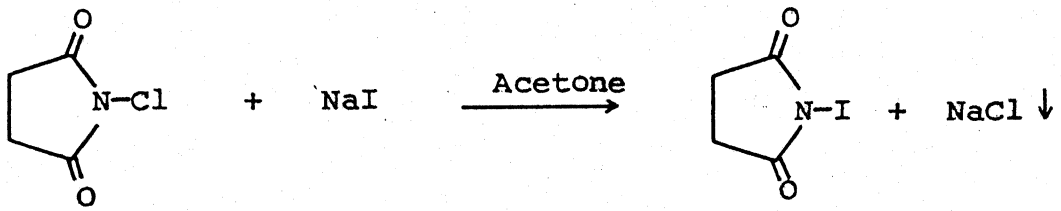
Thus, the above reactions clearly indicate that the new method for NIS preparation could be very useful in view of the fact that NIS could be either in situ generated or prepared prior to its use from NCS-NaI. The general difficulty with NIS, i.e. its sensitivity towards light and heat may be eliminated by adapting the simple procedure described here. Also, one can avoid the

use of expensive silver salts in its preparation and thus, makes it much cheaper compared to the commercially available NIS.

III.A(i).3 Experimental

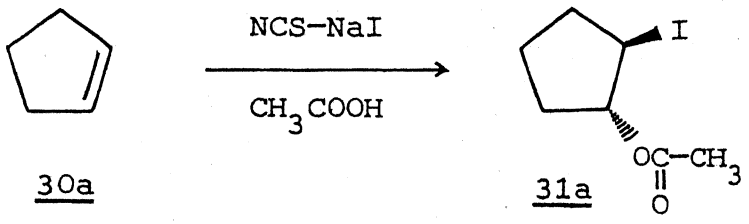
The details of the instruments used are the same as described in Section I.3. The solvents used were dried in the same manner as described in Sections I.3 and II.3. Enol silyl ethers 35a-c, 37 and 39 were prepared, following literature procedure,[23] from the corresponding ketones.

Preparation of N-iodosuccinimide (NIS)



N-Chlorosuccinimide (134 mg, 1 mmol) and sodium iodide (150 mg, 1 mmol) were dissolved separately in dry acetone (2.5 mL) and mixed together at room temperature. The resultant mixture was stirred for 15 min, then acetone (10 mL) was added to it and the precipitated sodium chloride was filtered. Evaporation of the solvent under vacuum gave almost pure NIS. Yield, 215 mg (95%). Analytical sample was obtained by recrystallizing it from dioxan-CCl_4 mixture, m.p. 198-200°C (lit[20], m.p. 200-201°C).

Preparation of trans-1-acetoxy-2-iodocyclopentane (31a)



30a 31a

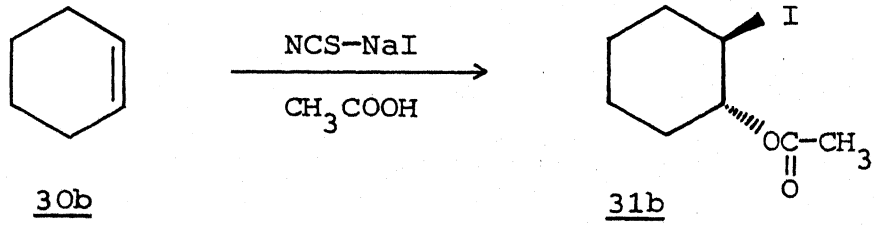
Equimolar amounts of NCS (295 mg, 2.2 mmol) and NaI (330 mg, 2.2 mmol) were dissolved separately in dry acetone (2.5 mL) and mixed together at room temperature. The resultant mixture was stirred for 10 min. then acetone (10 mL) was added to it and the precipitated NaCl was filtered. Acetone was evaporated completely under vacuum and the residue was suspended in chloroform (2 mL). It was treated with cyclopentene (100 mg, 1.47 mmol) dissolved in chloroform (1 mL) and acetic acid (0.17 mL, 2.9 mmol). After stirring at room temperature for 1 h, the mixture was diluted with ether (20 mL), washed with 2N sodium carbonate solution (10 mL), 5% sodium thiosulphate solution (10 mL), water (10 mL), brine (5 mL) and dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the product was purified by column chromatography [eluent, pet.ether:benzene (80:20)]. Yield, 345 mg (92%).

IR spectrum ν_{max}(neat): 1730 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.4-2.6 (m, 6H, CH_2), 2.0 (s, 3H, CH_3), 4.17 (m, 1H, C<u>H</u>-I), 5.26 (m, 1H, C<u>H</u>-OAc).

The reaction of cyclopentene (100 mg, 1.47 mmol), NIS (commercially available) (496 mg, 2.2 mmol) and CH_3COOH (0.17 mL, 2.4 mmol) in $CHCl_3$ (2 mL) at room temperature for 1 h gave 31a in 95 % yield.

Preparation of trans-1-acetoxy-2-iodocyclohexane (31b)



30b 31b

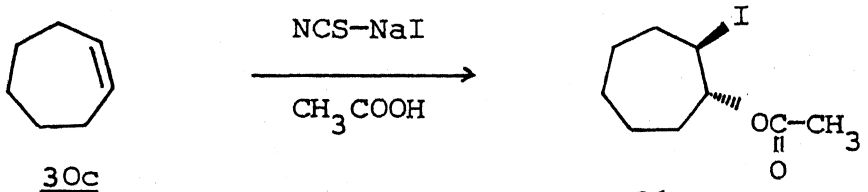
Following the above described procedure, the reaction of cyclohexene (100 mg, 1.22 mmol) with NCS (245 mg, 1.83 mmol), NaI (275 mg, 1.83 mmol) and CH_3COOH (0.14 mL, 2.44 mmol) in $CHCl_3$ (2 mL) for 1 h at room temperature gave crude 31b which was purified by column chromatography [eluent, pet.ether:benzene (90:10)]. Yield, 277 mg (92%).

IR spectrum ν_{max}(neat): 1730 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 2.10 (s, 3H, $COCH_3$), 4.10 (m, 1H, C<u>H</u>-I), 4.99 (m, 1H, C<u>H</u>-OAc).

The reaction of cyclohexene (100 mg, 1.22 mmol), NIS (commercially available) (412 mg, 1.83 mmol) and CH_3COOH (0.14 mL, 2.44 mmol) in $CHCl_3$ at room temperature for 1 h gave 31b in 97 % yield.

Preparation of trans-1-acetoxy-2-iodocycloheptane (31c)



30c 31c

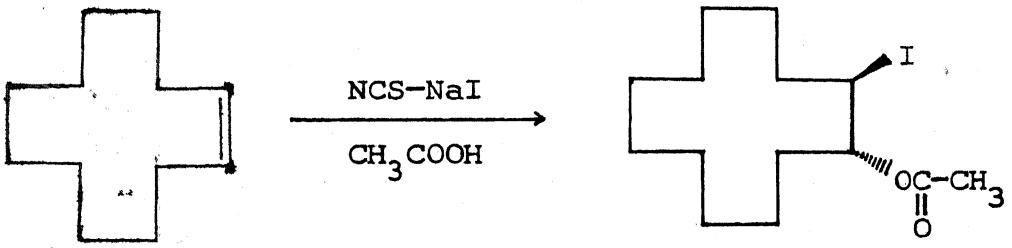
Following the procedure described for 31a, the reaction of cycloheptene (100 mg, 1.04 mmol), NCS (210 mg, 1.56 mmol), NaI (235 mg, 1.56 mmol) and CH_3COOH (0.12 mL, 2.08 mmol) in $CHCl_3$ (2 mL) at room temperature for 12 h gave crude 31c which was purified by column chromatography [eluent, pet.ether:benzene (95:5)]. Yield, 255 mg (87%).

IR spectrum ν_{max}(neat): 1730 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.63 (m, 10H, CH_2), 2.0 (s, 3H, $COCH_3$), 4.2 (m, 1H, C<u>H</u>-I), 4.93 (m, 1H, C<u>H</u>-OAc).

The reaction of cycloheptene (100 mg, 1.04 mmol) with commercial NIS (350 mg, 1.56 mmol) and CH_3COOH (0.12 mL, 2.08 mmol) at room temperature for 12 h gave 31c in 95 % yield.

Preparation of trans-1-acetoxy-2-iodocyclododecane (31d)



30d 31d

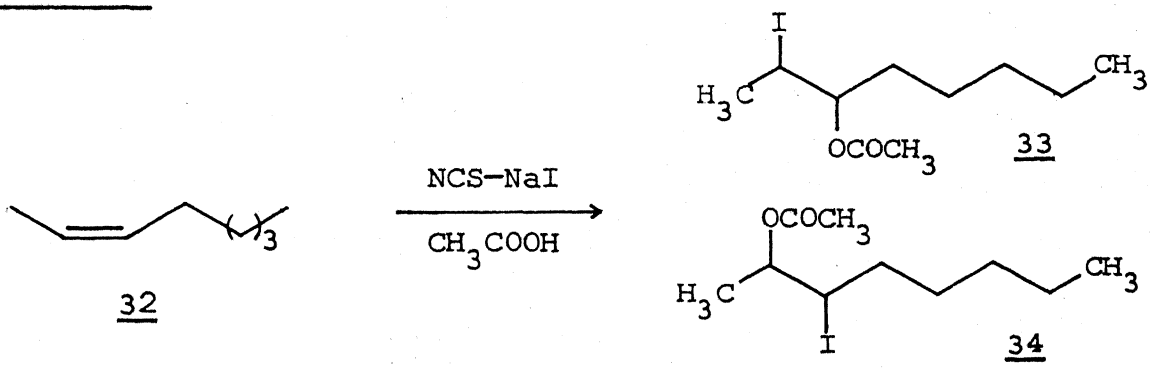
Following the procedure described for 31a, the reaction of cis-cyclododecene (200 mg, 1.2 mmol), NCS (242 mg, 1.8 mmol), NaI (270 mg, 1.8 mmol) and CH_3COOH (0.14 mL, 2.4 mmol) in $CHCl_3$ at room temperature for 12 h and then at 60°C for 2 h gave crude 31d which was purified by column chromatography [eluent, pet.ether: benzene (90:10)]. Yield, 370 mg (88%).

IR spectrum ν_{max}(neat): 1730 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.4 (m, 20H, CH_2), 2.05 (s, 3H, $COCH_3$), 4.26 (m, 1H, C<u>H</u>-I), 4.6 (m, 1H, C<u>H</u>-OAc).

The reaction of trans-cyclododecene (200 mg, 1.2 mmol) with commercially available NIS (405 mg, 1.8 mmol) and CH_3COOH (0.14 mL, 2.4 mmol) at room temperature for 12 h and then at 60°C for 2 h gave 31d in 89% yield.

Preparation of 3-acetoxy-2-iodooctane (33) and 2-acetoxy-3-iodooctane (34)



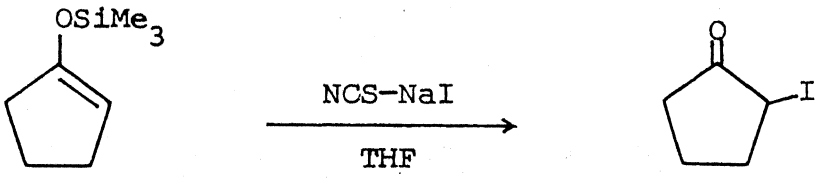
The reaction of cis-2-octene (200 mg, 1.79 mmol), NCS (360 mg, 2.69 mmol), NaI (403 mg, 2.69 mmol) and CH_3COOH (0.2 mL, 3.58 mmol) in $CHCl_3$ (2 mL) at room temperature for 12 h gave a mixture of iodoacetates 33 and 34 which was purified by column chromatography [eluent, pet.ether:benzene (90:10)]. Yield, 410 mg (77%).

IR spectrum ν_{max}(neat): 1725 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 0.9 (t, 3H, CH_3), 1.1–2.0 (m, 8H, CH_2), 1.3 and 1.83 (2d, J=6 Hz, 3H, CH_3), 2.03 and 2.06 (2s, 3H, $COCH_3$), 4.13 (m, 1H, C<u>H</u>–I), 4.75 (m, 1H, C<u>H</u>–OAc).

In a similar fashion, the reaction of 32 with commercially available NIS gave once again a mixture of 33 and 34 in the ratio 30:70 in 80% yield.

Preparation of α-iodocyclopentanone (36a)



Equimolar amounts of NCS (257 mg, 1.92 mmol) and NaI (288 mg, 1.92 mmol) were dissolved separately in dry acetone (2.5 mL) and mixed together at room temperature and stirred for 10 min. Complete removal of acetone under reduced pressure gave a residue which was suspended in anhydrous THF (5 mL) and enol silyl ether of cyclopentanone 35a (200 mg, 1.28 mmol) was added to the mixture maintained at 0°C and stirred for 30 min. It was then poured into a mixture of satd. aq. sodium bicarbonate (10 mL) and brine (10 mL), and extracted with petroleum ether (3 x 10 mL). The organic layers were combined and washed with 10 %sodium thiosulphate solution, (5 mL), water (5 mL), brine (5 mL) and dried over anhydrous sodium sulphate. Removal of solvent under vacuum gave a pale yellow liquid which was purified by column chromatography [eluent, pet. ether:benzene (95:5)]. Yield, 205 mg (76%).

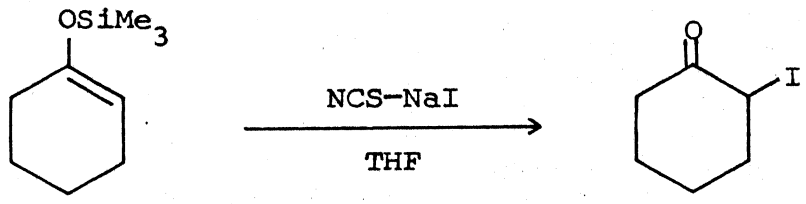
IR spectrum ν_{max}(neat): 1730 (C=O) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 2.24 (m, 6H, CH_2), 4.60 (m, 1H, CH-I).

Mass spectrum, m/e (rel.int.): 210 (65, M^+), 83 (100, M^+-I), 55 (100).

The reaction of 35a (200 mg, 1.28 mmol) with commercially available NIS (432 mg, 1.92 mmol) in THF at 0°C for 30 min gave 36a in 76 % yield.

Preparation of 2-iodocyclohexanone (36b)



35b 36b

Following the above described procedure the reaction of 35b (200 mg, 1.18 mmol) with NCS (235 mg, 1.75 mmol) and NaI (263 mg, 1.75 mmol) in THF at 0°C for 30 min gave a crude 36b which was purified by column chromatography [eluent, pet.ether:ether (90:10)]. Yield 220 mg (83%).

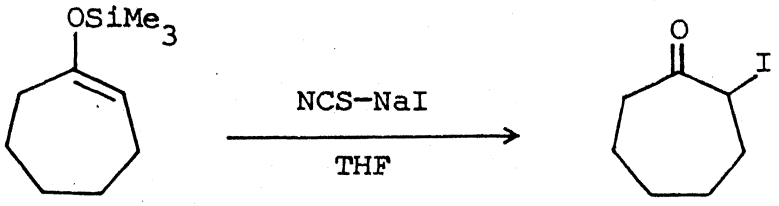
IR spectrum ν_{max}(neat): 1710 (C=O) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.50–2.35 (m, 7H, CH_2), 3.25 (m, 1H, CH–C–I), 4.73 (m, 1H, CH–I).

Mass spectrum, m/e (rel.int.): 224 (67, M^+), 97 (100, M^+–I), 55 (100).

In a similar fashion, the reaction of 35b (200 mg, 1.18 mmol) with commercial NIS (400 mg, 1.77 mmol) gave 36b in 84 % yield.

Preparation of 2-iodocycloheptanone (36c)



35c 36c

Following the procedure described for 36a, the reaction of 35c (100 mg, 6.54 mmol), NCS (108 mg, 0.81 mmol) and NaI (122 mg, 0.81 mmol) in THF at 0°C for 30 min gave crude 36c which was purified by column chromatography [eluent, pet.ether:ether (90:10)]. Yield, 110 mg (85%).

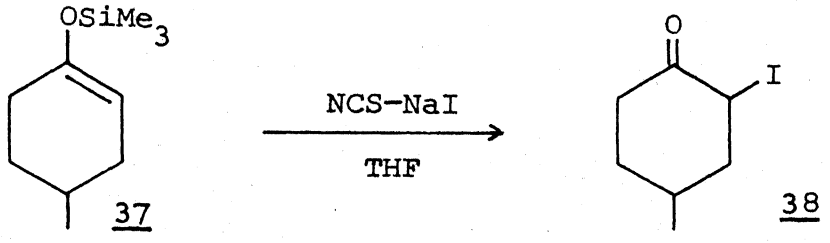
IR spectrum ν_{max}(neat): 1700 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.0–3.2 (m, 10H, CH_2), 4.46 (m, 1H, C<u>H</u>–I).

Mass spectrum, m/e (rel.int.): 238 (100, M^+), 111 (65, M^+–I), 55 (92).

In a similar fashion, the reaction of 35c (100 mg, 0.54 mmol) with commercial NIS (182 mg, 0.81 mmol) gave 36c in 86% yield.

Preparation of 2-iodo-4-methylcyclohexanone (38)



37 38

The reaction of 37 (100 mg, 0.54 mmol), NCS (108 mg, 0.81 mmol) and NaI (122 mg, 0.81 mmol) in THF at 0°C for 30 min gave crude 38. It was purified by column chromatography [eluent, pet. ether:ether (90:10)]. Yield, 95 mg (74%).

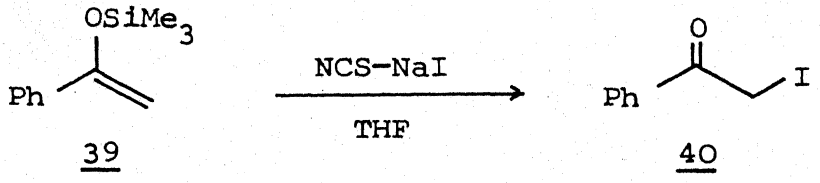
IR spectrum ν_{max}(neat): 1710 (C=O) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 0.8 (d, J=7 Hz, CH_3), 1.5-3.2 (m, 7H, CH_2 and CH), 4.75 (m, 1H, C<u>H</u>–I).

Mass spectrum, m/e (rel.int.): 238 (70, M^+), 111 (37, M^+–I), 55 (100).

The reaction of 37 (100 mg, 0.54 mmol) with commercial NIS (183 mg, 0.81 mmol) gave in 74% yield.

Preparation of 2-iodoacetophenone (40)



39 40

Following the produce described for 36a, the reaction of 39

(100 mg, 0.52 mmol), NCS (105 mg, 0.78 mmol), NaI (117 mg, 0.78 mmol) in THF for 30 min at 0°C gave crude 40. It was recrystallized from pet.ether 60–80°C. Yield, 90 mg (71%), m.p. 32–34°C (lit[14a], m.p. 34–34.5°C).

IR spectrum $\nu_{max}(CHCl_3)$: 1685 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 4.25 (s, 2H, CH_2–I), 7.28–7.65 (m, 3H, aromatic), 7.87–8.10 (m, 2H, aromatic).

Mass spectrum, m/e (rel.int.): 246 (18, M^+), 119 (100, M^+–I), 105 (20, M^+–CH_2I), 77 (100, $C_6H_5^+$).

The reaction of 39 (100 mg, 0.52 mmol) with commercial NIS (175 mg, 0.78 mmol) gave 40 in 72 %yield.

(ii) Synthesis of 1,4 and 1,5-dicarbonyl compounds from ene-diones and cyclopropyl diketones respectively using sodium iodide-chlorotrimethylsilane

III.A(ii)1 Introduction

Organo-silican reagents, particularly iodotrimethylsilane,[24] have found extensive use in organic synthesis. Iodotrimethylsilane is a neutral, hard-soft reagent. It contains silican as hard acid in the form of $Me_3Si^{\delta+}$ and iodide as a soft base in the form of $I^{\delta-}$. This reagent, therefore, reacts very readily with organic compounds containing oxygen in the form of a nucleophile (a hard base) forming a strong silican-oxygen bond. The iodide ion on the other hand can act as a strong nucleophile if needed in the reaction. This reactivity of iodotrimethylsilane has been exploited to carry out a large number of synthetically useful transformations.

Iodotrimethylsilane has been prepared by a number of methods.[25] Thus for example, it can be conveniently prepared by the reaction of hexamethyltisiloxane with aluminium iodide,[25a] by reacting phenyltrimethylsilane with iodine[25b] and also from the reaction of allyltrimethyl silane with iodine.[25c] However, since $ISiMe_3$ is not stable enough to be stored for a longer period of time, its *in situ* generation has been explored. Olah et al.[26a] and at the same time

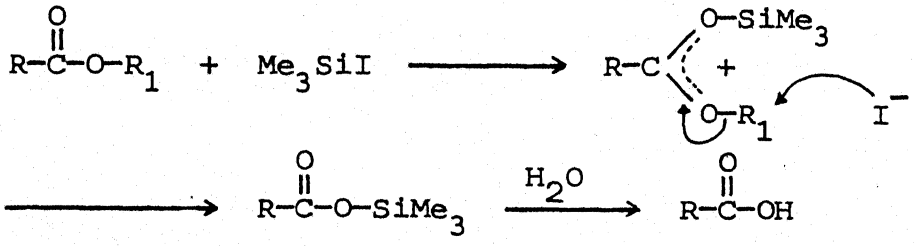
Morita et al.[26b] have developed a simple and inexpensive method for its in situ generation, from sodium iodide and chlorotrimethylsilane in acetonitrile. A mixture of sodium iodide and chlorotrimethylsilane in acetonitrile was found to form a complex 43 which is the in situ equivalent of iodotrimethylsilane. This reagent

$$Me_3SiCl + NaI \xrightarrow{CH_3C\equiv N} [CH_3-C\equiv\overset{+}{N}-SiMe_3]I^- + NaCl$$

43

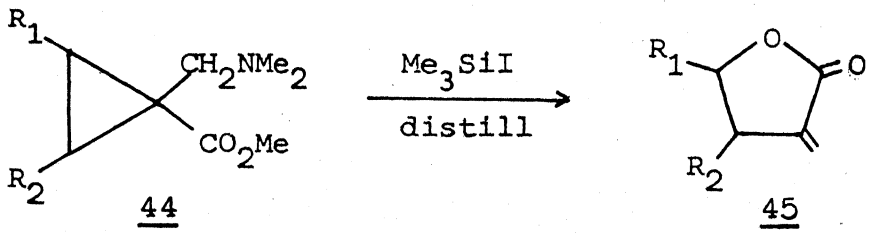
system was found to be better than pure iodotrimethylsilane in many of its reactions with organic substrates.

Iodotrimethylsilane was found to be an efficient reagent for hydrolysis of esters strictly under neutral conditions[27] (Scheme III.A.12). An elegant application of such hydrolysis of



Scheme III.A.12

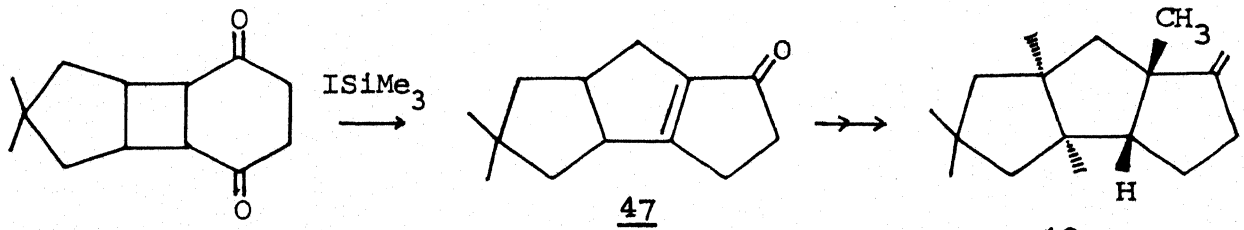
esters has been demonstrated in the synthesis of α-methylene-ν-butyrolactones 45[28] (Scheme III.A.13).



44 45

Scheme III.A.13

This reagent has been used further for the conversion of epoxides to olefins,[29] alcohols to iodides,[30] sulphoxides to sulphides,[31] and for the cleavage of ethers to alcohols.[32] Non-aqueous hydrolysis of acetals has also been done using this reagent system.[33] Iodotrimethylsilane has been used in a simple synthesis Hirsutene (48)[34] (Scheme III.A.14).

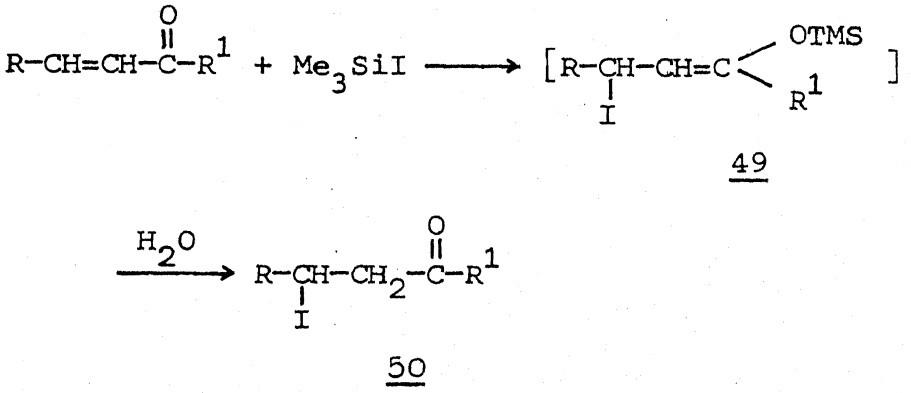


46 47 48

Scheme III.A.14

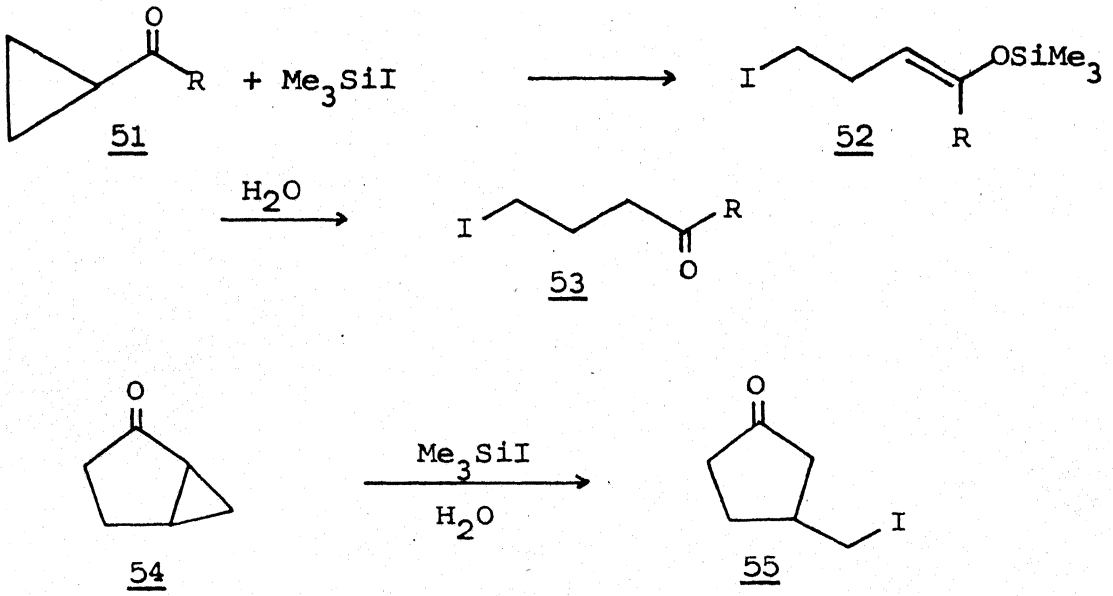
When α,β-unsaturated ketones were treated with iodotrimethylsilane, Michael addition products 49 were formed, which on hydrolysis gave

β-iodoketones 50[35] (Scheme III.A.15). This observation was



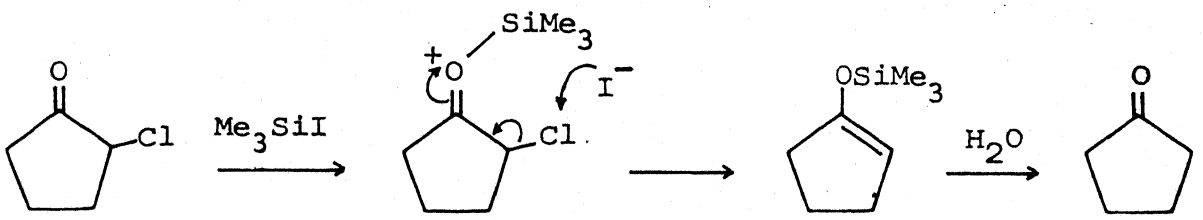
Scheme III.A.15

extended by Miller et al.[36] to cyclopropyl ketones to give ν-iodo-ketones (Scheme III.A.16).



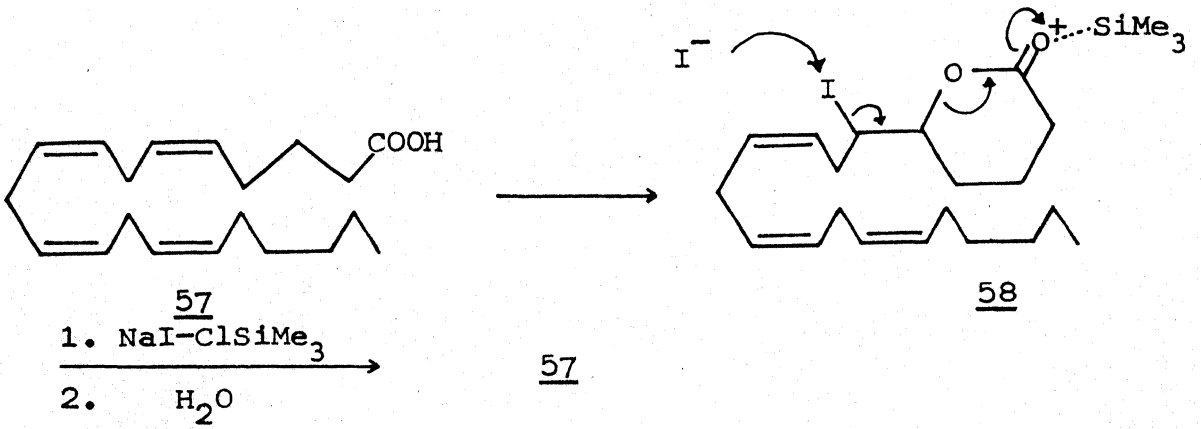
Scheme III.A.16

Olah and Vankar[37] observed an interesting dehalogenation reaction of α-haloketones to ketones using sodium iodide-chlorotrimethylsilane in acetonitrile. This reaction and the mechanism involved, as postulated, is shown in Scheme III.A.17. This



Scheme III.A.17

principle was applied by Corey[38] in the purification and separation of arachidonic acid from a commercial mixture of acids (Scheme III.A.18). Arachidonic acid is the only fatty acid present in the



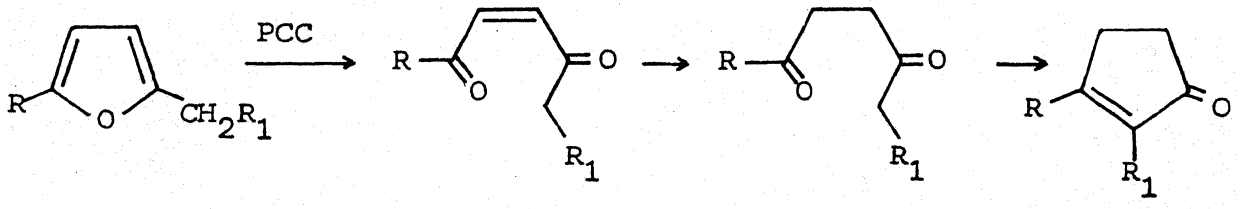
Scheme III.A.18

impure commercial mixture of acids that is capable of forming iodolactone. Arachidonic acid was regenerated from 58, after separating

it from the mixture, by treatment with sodium iodide and chlorotrimethylsilane followed by hydrolysis.

A combination of the above described two reactions, viz., addition of iodotrimethylsilane to α,β-unsaturated ketones (Scheme III.A.15) and dehalogenation of α-haloketones (Scheme III.A.17) has been successfully applied by us for the synthesis of 1,4 and 1,5-diketones starting from ene-diones and cyclopropyldiketones respectively. This is described in the ''results and discussion'' section of this chapter.

Importance of 1,4-diketones as valuable intermediates in the synthesis of natural products having cyclopentanoid ring systems, is well documented.[39] The reduction of the double bond in conjugated ene-diones provides a convenient method for the synthesis of 1,4-diketones. One of the recently developed methods[40] to produce such compounds involves the conversion of furan derivatives to ene-dicarbonyl compounds followed by the reduction of double bond (Scheme III.A.19).



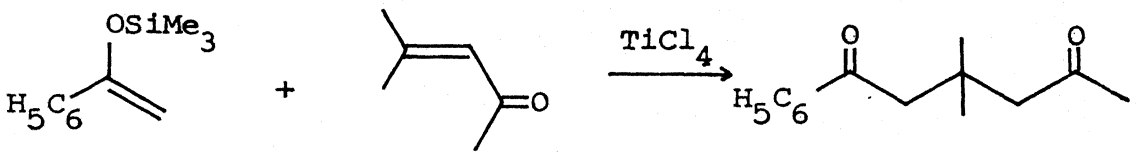
59 60 61 62

Scheme III.A.19

Various reducing systems have been utilized to bring about the reduction of conjugated ene-diones to 1,4-dicarbonyl compounds. For example, zinc-acetic acid combination has been used for the reduction of ene-diones to 1,4-diketones in steroid chemistry.[41] Chromium(II) chloride[42] has also been utilized for this purpose McMurry[43] has reported a fairly simple and general reduction procedure for conjugated ene-diones using low-valent titanium reagent. Although a variety of substrates have been reduced by aqueous titanous chloride, ene-diesters were found resistant to reduction. Zinc-zinc chloride combination has been utilized by Toda et al.[44] for ene-diones reduction under mild reaction conditions. Piancatelli et al.[45] have developed a simple reagent system viz., NaI and conc. HCl for the reduction of ene-diones to 1,4-dicarbonyl compounds. Large excess of concentrated hydrochloric acid was used in this conversion, moreover, double bonds flanked by carboxylic acid groups and esters were not reduced by this reagent system. Earlier from our laboratory two reagents systems viz. NaI-$BF_3.Et_2O$ and Zn-$ClSiMe_3$ have been reported[46] for the conversion of ene-dicarbonyl compounds to 1,4-diketones under mild reaction conditions.

Synthesis of 1,5-dicarbonyl compounds are useful in the synthesis of six membered cyclic compound. Addition of carbonyl compounds in the presence of bases, to α,β-unsaturated carbonyl compounds is one of the general methods to prepare 1,5-dicarbonyl compounds. Thus, addition of enol silyl ethers to α,β-unsaturated

ketones and esters in the presence of catalytic amount of $TiCl_4$ has been reported to be a useful method[47] (Scheme III.A.20).



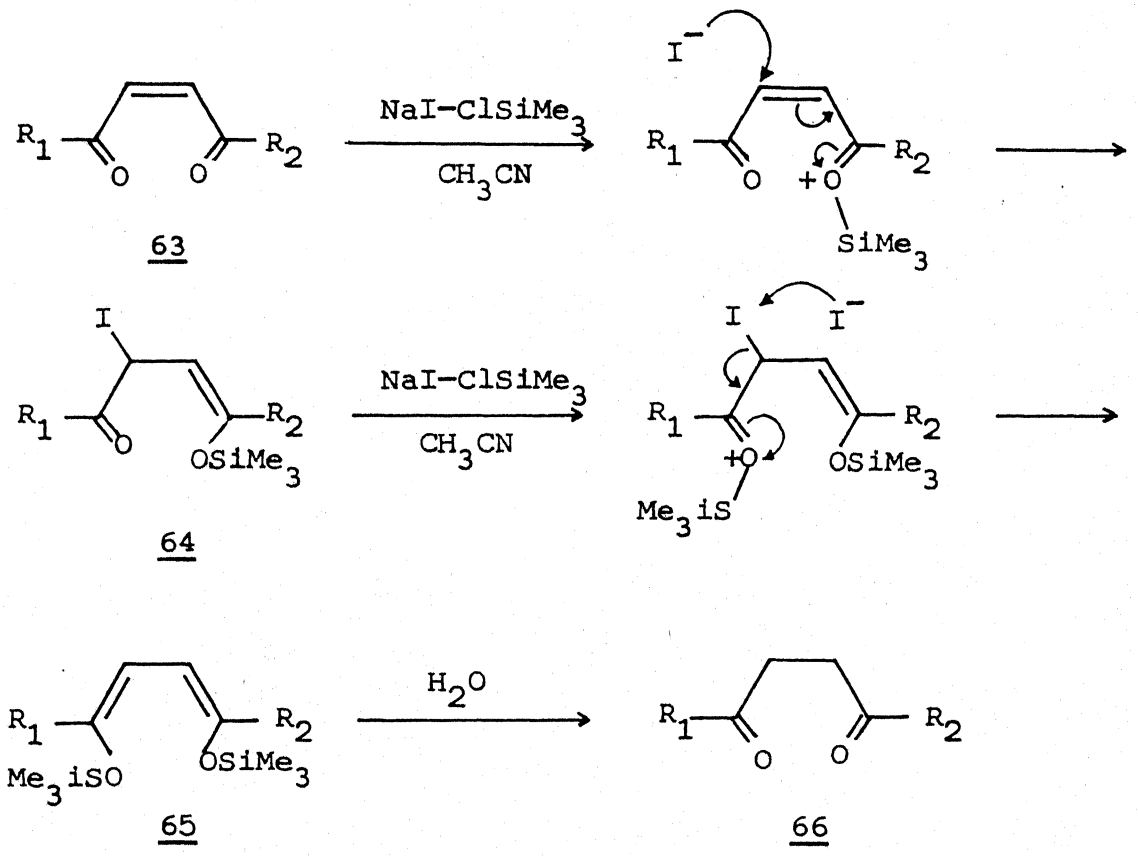
Scheme III.A.20

Interestingly there is no report in the literature, to our knowledge, for its preparation by the reductive ring opening of cyclopropyl diketones.

III.A(ii)2 Results and Discussions

The literature concerning the reduction of ene-diones involves either low yielding methods or the use of strongly acidic (protic or Lewis acid) reagent systems. Hence, development of a method under neutral and mild conditions is required. We have utilized $NaI-ClSiMe_3$, a neutral, hard-soft reagent, for the conversion of ene-diones to 1,4-dicarbonyl compounds and cyclopropyl diketones to 1,5-dicarbonyl compounds. It was expected, on the basis of HSAB principle, that an ene-dione would coordinate through oxygen a hard base, with the hard acid $^{+}SiMe_3$, followed by the

attack of the soft nucleophile, i.e. I^- on the soft β-carbon resulting in the formation of an intermediate 64 (Scheme III.A.21).

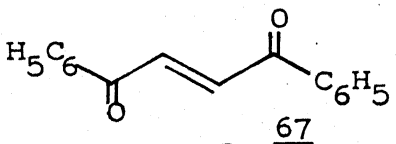
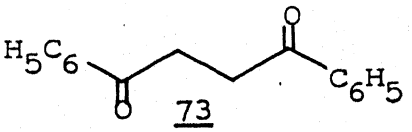
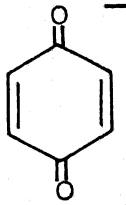
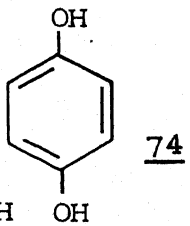
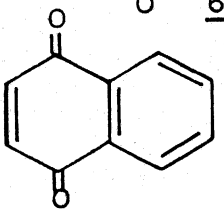
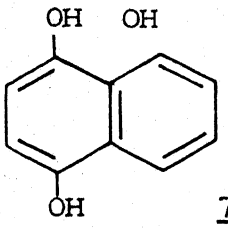
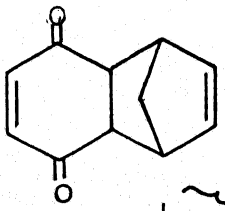
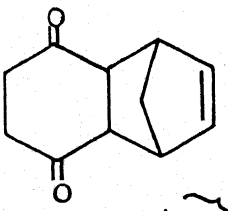
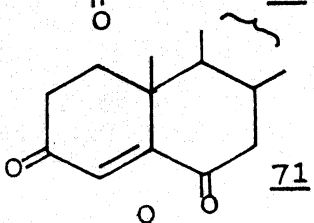
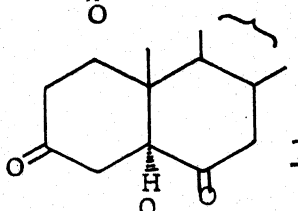
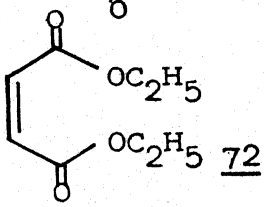
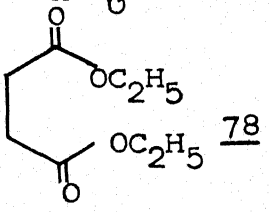


Scheme III.A.21

As it is known in the literature[37] that α-haloketones are reduced to the corresponding ketones, using this reagent system via enol silyl ethers, it was expected that the intermediate 64 should yield another intermediate 65 in the presence of an excess of $NaI-ClSiMe_3$ as shown in Scheme III.A.21. This intermediate 65 would give 1,4-diketone 66 upon aqueous treatment.

It was indeed found that a number of ene-diones 67-72 could be converted into the corresponding reduced products 73-78 using this reagent system in 89-96% yields (Table III.A.3). Thus,

Table III.A.3

Substract	Product	% Yield
 67	 73	94
 68	 74	91
 69	 75	89
 70	 76	90
 71	 77	89
 72	 78	96

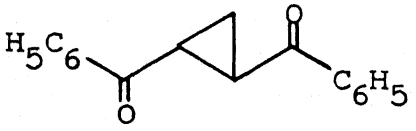
dibenzoylethylene(67)was reacted with NaI-chlorotrimethylsilane in acetonitrile at room temperature for 5 h to give the corresponding reduced product viz., dibenzoylethane(73)in 94% yield. In a similar fashion, benzoquinone(68)and napthaquinone(69)gave hydroquinone(74)and 1,4-dihydroxynapthalene (75)in 91% and 89% respectively.

The ene-dione 70 was prepared according to literature procedure,[48] by reacting benzoquinone with cyclopentadiene, whose IR spectrum showed a strong absorption at 1660 ($\nu_{C=O}$) cm^{-1}. Δ^4-Cholestene-3,6-dione(71)was prepared according to literature procedure[49] by oxidizing cholesterol with $Na_2Cr_2O_7$ in 40% yield.

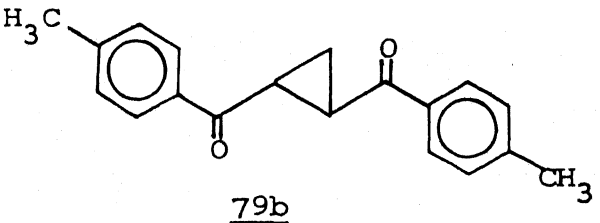
When 70 was treated with NaI-chlorotrimethylsilane in acetonitrile at room temperature for 15 min., the corresponding reduced product 76 was obtained in 90% yield. Its IR spectrum showed a strong absorption at 1700 ($\nu_{C=O}$) cm^{-1} indicating the absence of conjugation with the carbonyl groups. Its ^1H NMR spectrum showed absorptions at δ 1.17-1.60 (m, 2H, bridge CH_2), 2.01-2.90 (m, 4H, $COCH_2$), 3.07 (d, 2H, COCH), 3.40 (m, 2H, allylic), 6.1 (m, 2H, olefinic). The spectral characteristics are in accordence with the structure 76. The ene-dione 71 was reacted with NaI-$ClSiMe_3$ to give the reduced product 77 in 89% yield. Its IR spectrum showed strong absorption at 1705 cm^{-1} and its ^1H NMR spectrum showed absence of vinylic proton (cf. experimental section).

Further, it was found that even diester, i.e., diethyl maleate (72) was reduced to diethyl succinate using this reagent system. Interestingly, under the experimental conditions, the ester functionality is unaffected.

The substrates chosen for the synthesis of 1,5-diketones from cyclopropyl diketones are 79a,b. These substrates were prepared according to literature procedure[50] in 73 % and 71 % yields



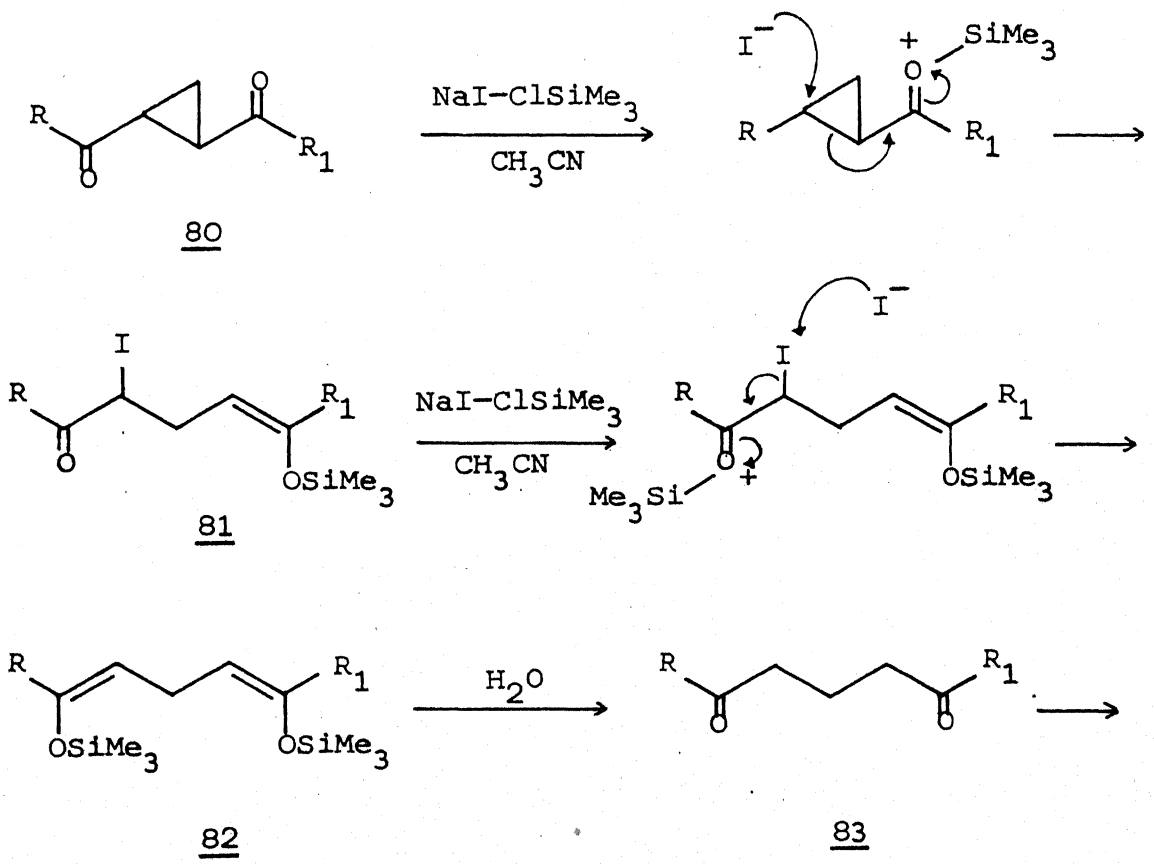
79a



79b

respectively. It was expected on the basis of literature and also from our own experience that Me_3Si^+ portion of Me_3SiI would coordinate with hard oxygen. Subsequent attack of soft iodide ion on the soft carbon of the cyclopropyl ring next to the other carbonyl group (because of the electrophilic nature of that carbon), should result in the formation of the intermediate 81 which could be converted into another intermediate 82 with another equivalent of $NaI-ClSiMe_3$ (Scheme III.A.22). This intermediate 82 would give 1,5-diketone upon hydrolytic work up.

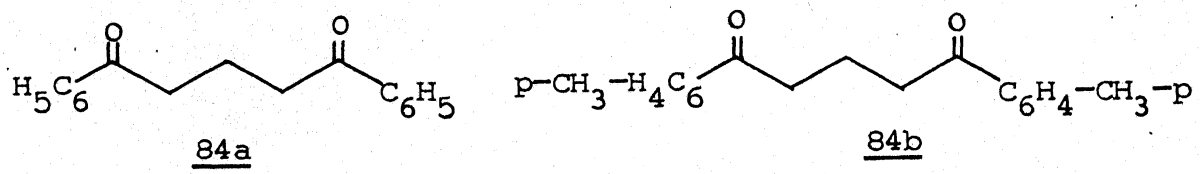
We have, indeed, converted cyclopropyl diketones 79a,b to their corresponding 1,5-dicarbonyl compounds 84a,b in 92 % and 98 %



80 81 82 83

Scheme III.A.22

yields respectively. The spectral charateristics of these products 84a,b were comparable with authentic samples (cf. experimental section).



84a 84b

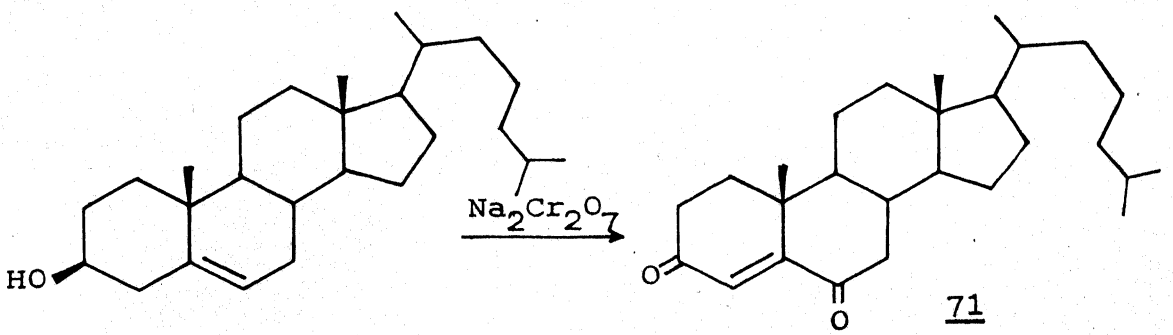
Thus, the reduction of ene-diones to 1,4-dicarbonyl compounds using NaI-ClSiMe$_3$ was carried out under essentially neutral and mild

reaction conditions. We have also shown, for the first time, the reductive cleavage of cyclopropyl ring to give 1,5-dicarbonyl compounds using this reagent system under neutral and mild reaction conditions and in high yields.

III.A.ii.3 Experimental

The details of the instruments are the same as described in Section I.3. The solvents used were dried in the same manner as described in Sections I.3 and II.3. Dibenzoylethylene (67) was prepared by the known literature procedure[51] by Friedel Crafts reaction of fumaroyl chloride with benzene. Δ^4-Cholestene-3,6-dione (71) and the benzoquinone cyclopentadiene adduct 70 were also prepared by known procedures as described below.

Preparation of Δ^4-cholestene-3,6-dione (71)

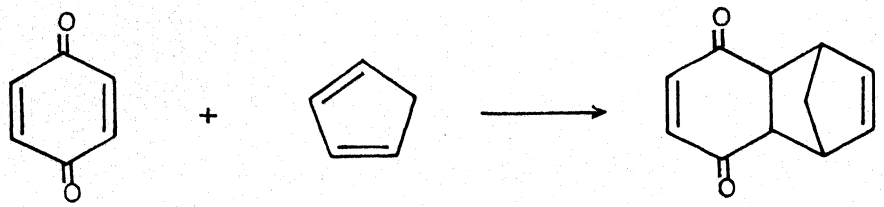


71

Cholesterol (2.0 g, 5 mmol) was dissolved in benzene (18 mL) by warming, and the solution was then cooled to 20°C. Glacial acetic

acid (18 mL) was then added to it and the mixture cooled to 15°C. A solution of $Na_2Cr_2O_7$ (prepared by dissolving 5.12 g of $Na_2Cr_2O_7$ in 18 mL of acetic acid by warming and then cooling to 15°C) was added slowly to the cholesterol solution at 15°C and the mixture allowed to cool in a refrigerator for 48 h. The mixture was then extracted with petroleum ether (40-60°C) (3 x 10 mL) and the combined organic layers washed once with water (10 mL). The organic layer was shaken with 10 mL of Claisen's alkali (prepared by dissolving 14 g of KOH pellets in 10 mL of distilled water, followed by addition of 40 mL of methanol), the lower aqueous layer was separated and treated with water (20 mL), ice (50 g), 30% HCl (16 mL), and ether (30 mL). The organic layer was separated and the aqueous layer extracted with ether (2 x 10 mL). The organic layer was washed with 5% $NaHCO_3$ (10 mL), water (10 mL), brine (10 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent and recrystallization of the residue from methanol gave 71. Yield 0.92 g (40%), m.p. 118-120°C (lit[49], m.p. 124-125°C).

Preparation of the Diels-Alder adduct 70



70

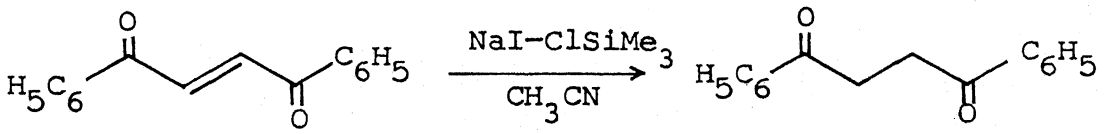
p-Benzoquinone (2.0 g, 18 mmol) was dissolved in 25 mL

absolute ethanol, cooled to 10°C and cyclopentadiene (1.19 g, 18 mmol) added slowly during 15 min. The reaction mixture was then stirred at room temperature for additional 30 min and then ethanol evaparated under reduced pressure to give a crude product. Recrystallization of the residue from petroleum ether gave 70. Yield 1.56 g (50%), m.p. 72-73°C (lit[48], m.p. 75-76°C).

General procedure for the reaction of ene-diones with sodium iodide-chlorotrimethylsilane

To a stirred solution of the ene-dione (0.5 mmol) and sodium iodide (1.5 mmol) in dry acetonitrile (5 mL) at room temperature was added chlorotrimethylsilane (1.5 mmol) in 1 mL of acetonitrile. The reaction mixture was stirred at room temperature. After completion of the reaction the mixture was poured in to cold water (10 mL), treated with 10 %sodium thiosulphate solution and extracted with dichloromethane (3 x 10 mL). The combined extracts were washed with water (2 x 10 mL),brine (10 mL) and then dried over anhydrous sodium sulphate. Evaporation of the solvent gave almost pure reduced products which were further purified by recrystallization or chromatography.

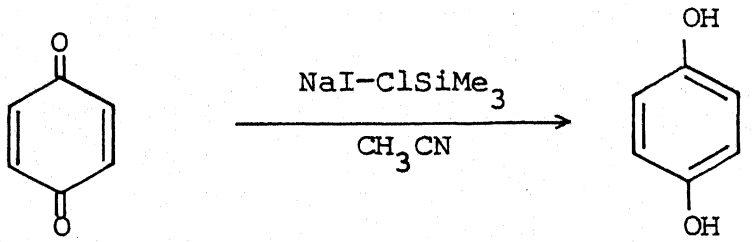
Preparation of 1,2-dibenzoylethane (73)



67 73

The reaction of 67 (100 mg, 0.42 mmol) with NaI (190 mg, 1.26 mmol) and chlorotrimethylsilane (0.16 mL, 1.26 mmol) in CH_3CN (5 mL) at room temperature for 5 h gave crude 73 which was purified by recrystallizing from ethanol. Yield 95 mg (94%), m.p. 143-145°C (lit[52], m.p. 145°C).

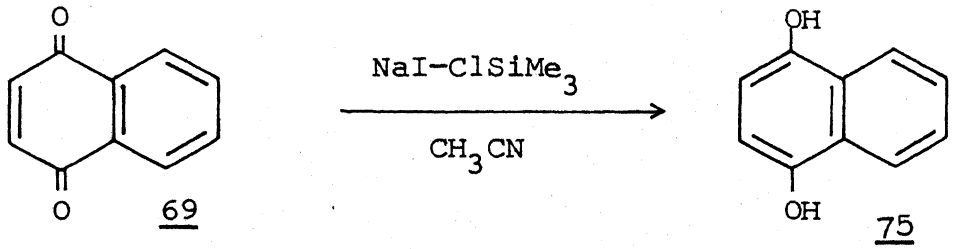
Preparation of hydroquinone (74)



68 74

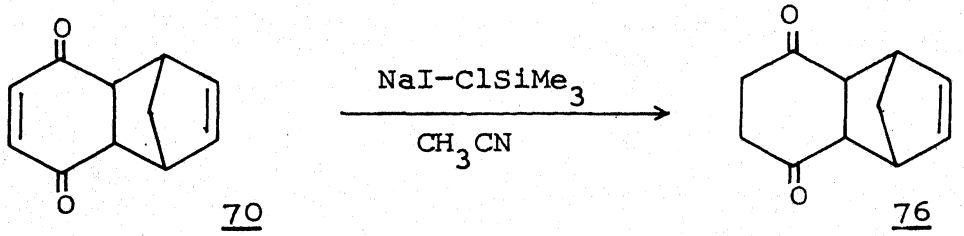
The reaction of 68 (108 mg, 1 mmol) with NaI (375 mg, 2.5 mmol) and chlorotrimethylsilane (0.32 mL, 2.5 mmol) in CH_3CN at room temperature for 4 h gave 74. It was recrystallized from hot water. Yield 100 mg (91%), m.p. 170-172°C (lit[52], m.p. 171°C).

Preparation of 1,4-dihydroxynaphthalene (75)



Following the general procedure for ene-diones reduction, the reaction of 69 (100 mg, 0.63 mmol) with NaI (285 mg, 1.9 mmol) and chlorotrimethylsilane (0.24 mL, 1.9 mmol) in CH_3CN (3 mL) at room temperature for 48 h gave 75. The crude product was recrystallized from water. Yield 90 mg (89%). m.p. 174-176°C (lit[52], m.p. 176°C).

Preparation of (76)



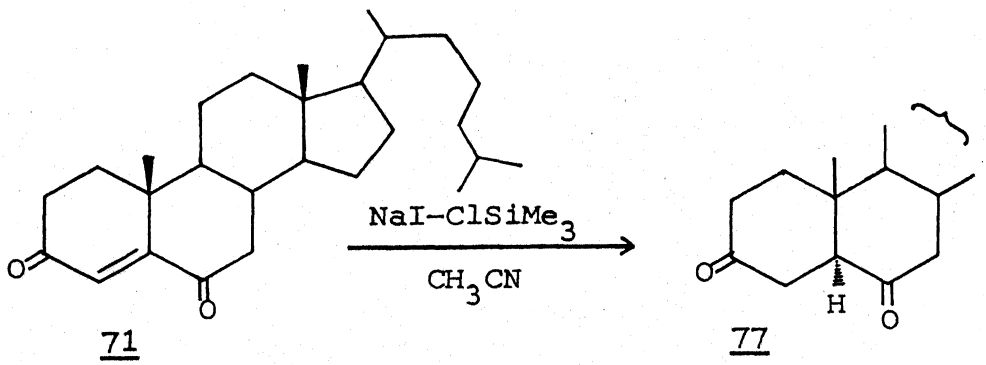
The reaction of 70 (100 mg, 0.57 mmol) with NaI (260 mg, 1.72 mmol) and chlorotrimethylsilane (0.22 mL, 1.72 mmol) in CH_3CN at room temperature for 15 min. gave a crude product. It was purified by preparative thin layer chromatography [eluent:benzene] to give 76 as a thick liquid. Yield 90 mg (90%).

IR spectrum ν_{max}(neat): 1700 (C=O) cm^{-1}.

^1H NMR spectrum ($CDCl_3$): δ 1.17–1.60 (m, 2H, bridge CH_2), 2.01–2.90 (m, 4H, $COCH_2$), 3.07 (d, 2H, CH–CO), 3.40 (m, 2H, allylic), 6.10 (m, 2H, vinylic).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 75.0; H, 6.82. Found: C,75.10; H, 6.75.

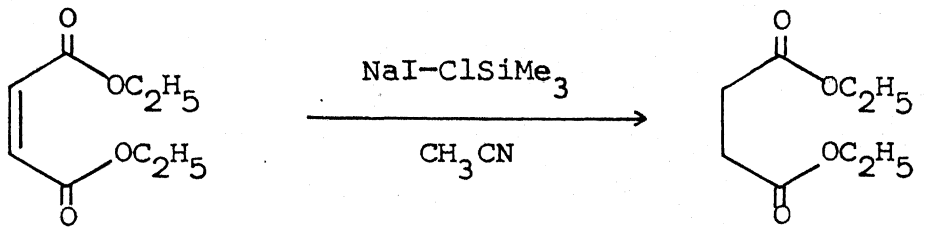
Preparation of 5α-cholestane-3,6-dione (77)



71 77

The reaction of 71 (200 mg, 0.5 mmol) with sodium iodide (225 mg, 1.5 mmol), chlorotrimethylsilane (0.19 mL, 1.5 mmol) in acetonitrile (5 mL) at room temperature for 5 h gave a crude product which was purified by recrystallization using methanol. Yield 180 mg (89%), m.p. 170–171°C (lit[45], m.p. 172°C).

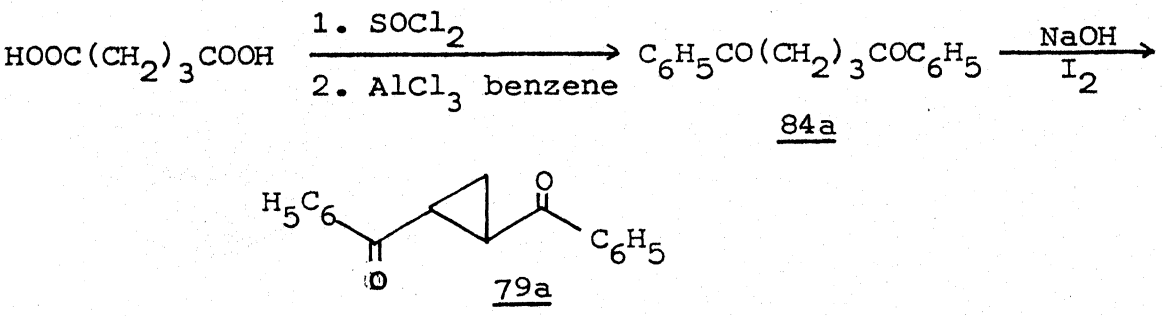
Preparation of diethyl succinate (78)



72 78

Following the general procedure for ene-dione reduction, the reaction of diethyl maleate 72 (200 mg, 1.16 mmol), sodium iodide (365 mg, 2.44 mmol) and chlorotrimethylsilane (0.31 mL, 2.44 mmol) in CH_3CN (5 mL) at room temperature for 36 h gave a crude product which was purified by distillation. Yield 194 mg (96%), b.p. 125°C/20 mm (lit[53], b.p. 105°C/15 mm).

Preparation of 1,2-dibenzoylcyclopropane (79a)



84a 79a

Glutaryl chloride [prepared from glutaric acid (5 g, 0.038 mol) and thionyl chloride (8.2 mL, 0.112 mol)]was added slowly to a

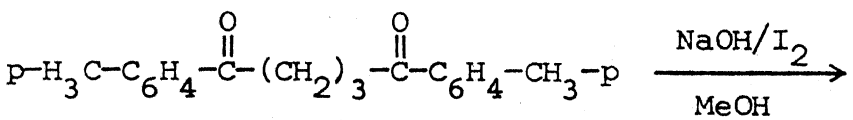
stirred suspension of $AlCl_3$ (15 g, 0.1 mol) in benzene (50 mL) at 5-10°C. After the addition, the reaction mixture was allowed to stir at room temperature for 2 h. Then, it was poured into a mixture of crushed ice (50 g) and conc. HCl (10 mL), the organic layer was separated and the aqueous layer extracted with benzene (2 x 15 mL). The combined organic layer was washed with 10% Na_2CO_3 solution (20 mL), water (25 mL), brine (10 mL) and dried over anhydrous sodium sulphate. After evaporating the solvent, the resídue was recrystallized from ethanol. Yield 5.5 g (57%), m.p. 67-68°C (lit[52], m.p. 67.5°C).

1,3-Dibenzoylpropane (1 g, 4.0 mmol) was added to a mixture of NaOH (0.32 g, 8.0 mmol) in methanol (15 mL) and warmed to 45°C with stirring to dissolve the diketone. It was allowed to cool to room temperature and a solution of iodine (1 g, 4.0 mmol) in methanol (8 mL) was added slowly. After the addition was completed the resultant solution was stirred at room temperature for 1.5 h. After removal of methanol, the residue was diluted with CH_2Cl_2 (15 mL) washed with 10 $NaHCO_3$ (10 mL), water (10 mL), brine (5 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude product which was purified by recrystallization from methanol. Yield 730 mg, (73%), m.p. 100-102°C (lit[50], m.p. 102-103°C).

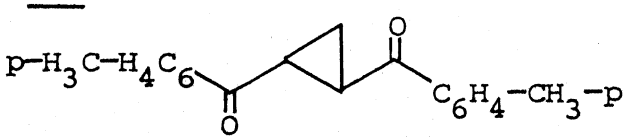
IR spectrum ν_{max}(KBr): 1660 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.75 (t, 2H, J=6 Hz, CH_2), 3.32 (t, 2H, J=6 Hz, C<u>H</u>-CO), 7.5 (m, 6H, aromatic), 8.05 (m, 4H, aromatic).

Preparation of 1,2-di(p-methyl)benzoylcyclopropane (79b)



84b



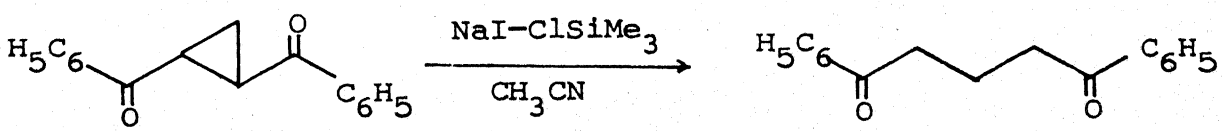
79b

Following the procedure for 79a, the reaction of 84b (1 g, 3.57 mmol) with NaOH (72 mg, 1.8 mmol) and iodide (830 mg, 3.57 mmol) in methanol (15 mL) at room temperature for 2 h gave 79b which was recrystallized from methanol. Yield 700 mg (71%), m.p. 108-110°C.

IR spectrum ν_{max}(KBr): 1660 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.78 (t, 2H, J=6 Hz, CH_2), 2.5 (s, 6H, CH_3), 3.42 (t, 2H, J=6 Hz, COCH), 7.35 (d, 2H, J=7.5 Hz, aromatic), 8.05 (d, 2H, J=7.5 Hz, aromatic).

Preparation of 1,3-dibenzoylpropane (84a)



79a 84a

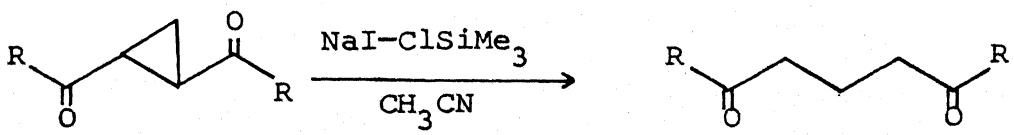
Following the general procedure for ene-dione reduction, the

reaction of 79a (100 mg, 0.4 mmol) with NaI (180 mg, 1.2 mmol) and chlorotrimethylsilane (0.15 mL, 1.2 mmol) in CH_3CN (3 mL) at room temperature for 1.5 h gave a crude product which was purified by recrystallization from ethanol. Yield 96 mg (92%), m.p. 67-68°C (lit[52], m.p. 67.5°C).

IR spectrum ν_{max}(KBr): 1680 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 2.18 (m, 2H, CH_2), 3.12 (t, 4H, J=6 Hz, $COCH_2$), 7.6 (m, 6H, aromatic), 8.5 (m, 4H, aromatic).

Preparation of 1,3-di(p-methylbenzoylpropane (84b)



79b 84b

R = C_6H_4-CH_3-p

Following the general procedure for ene-dione reduction, the reaction of 79b (100 mg, 0.36 mmol) with sodium iodide (162 mg, 1.08 mmol), and chlorotrimethylsilane (0.14 mL, 1.08 mmol) in CH_3CN (3 mL) at room temperature for 1 h gave almost pure product. It was further recrystallized from ethanol. Yield 100 mg (98%), m.p. 102-104°C.

IR spectrum ν_{max}(KBr): 1680 (C=O) cm^{-1}.

^{1}H NMR spectrum (CCl_4): δ 2.15 (t, 2H, J=6 Hz, CH_2), 2.4 (s, 6H, CH_3), 3.0 (t, 4H, J=6 Hz, $COCH_2$), 7.2 (d, 2H, J=7.5 Hz, aromatic), 7.88 (d, 2H, J=7.5 Hz, aromatic).

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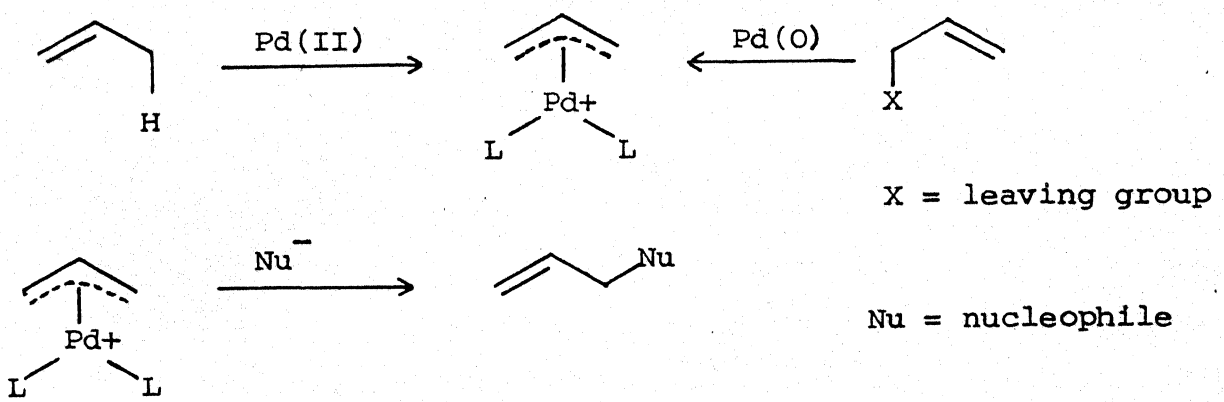
PART - B

TETRAKIS(TRIPHENYLPHOSPHINE)PALLADIUM(O) CATALYZED ALLYLIC ALKYLATION OF SOME SUBSTITUTED ALLYL ACETATES

III.B.1 Introduction

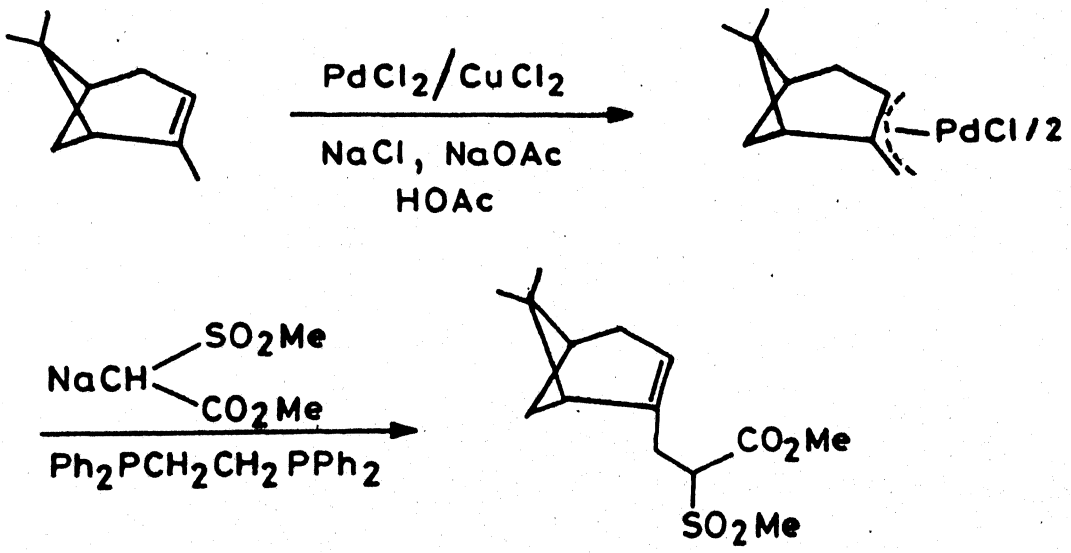
Allylic functionalization using π-allylpalladium complexes is a useful synthetic method in organic chemistry. π-Allylpalladium complexes have been generated either from an alkene using Pd(II) salts or from various allylic compounds such as allyl acetate and allyl carbonates using Pd(0) compounds. These π-allylpalladium complexes have been found to undergo reactions with variety of nucleophiles to give allyl functionalized compounds (Scheme III.B.1). Remarkable progress has been made in the chemistry



Scheme III.B.1

of π-allylpalladium complexes and their application to organic synthesis in the last 15 years.[1]

An example of the formation of π-allylpalladium complex from an alkene and its subsequent reaction with a nucleophile is shown in Scheme III.B.2. Allylic functionalization of alkenes via

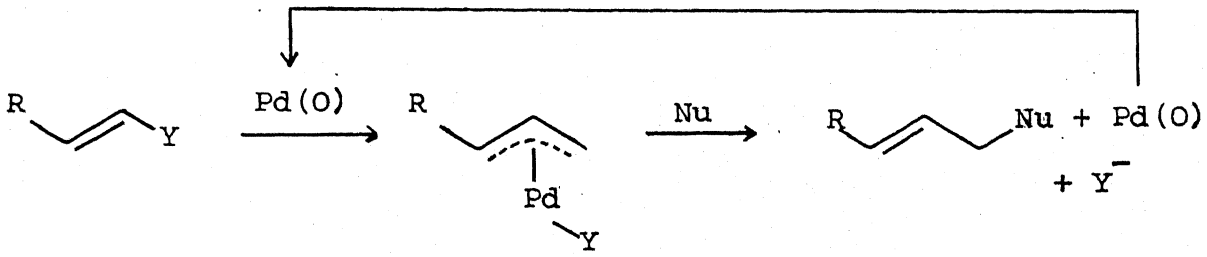


Scheme III.B.2

π-allylpalladium complexes require stoichiometric amounts of palladium compounds and hence it is an expensive method.

The most important method of generating π-allyl complexes 1 is the oxidative addition of an allyl derivative to Pd(0).[2] Interesting feature of this reaction is that the π-allyl complexes formed *in situ* as intermediates can be reacted with nucleophiles without being isolated and Pd(0) is regenerated, thus, making the

whole process a catalytic cycle (Scheme III.B.3). Allyl acetates



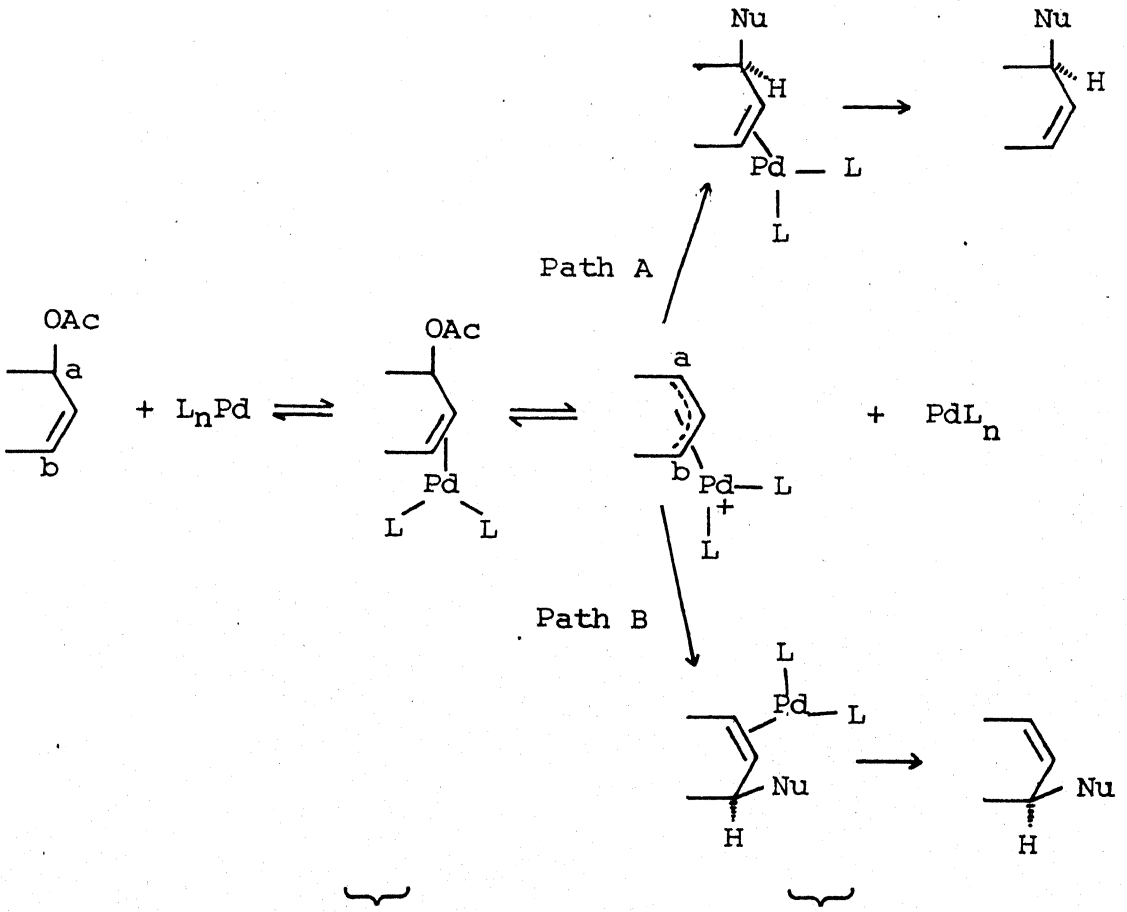
Y = $R\overset{O}{\overset{\|}{C}}O$, $RO\overset{O}{\overset{\|}{C}}O$, $R_2N\overset{O}{\overset{\|}{C}}O$, RO, $(RO)_2\overset{O}{\overset{\|}{P}}O$, NR_2, NO_2, SO_2R, NR_3X, SR_2X, Cl

Scheme III.B.3

have been found to be the most popular substrates, because of their stability and ease of preparation.

The catalytic cycle consists of an initial activation stage to form the π-allyl complex and a substitution stage to convert this complex to the final product (Scheme III.B.4). The activation stage consists of prior coordination of a coordinatively unsaturated palladium(0) species with the alkene on the face opposite that of the leaving group. The high electron density of the palladium then initiates disengagement of the leaving group to generate the π-allyl cationic intermediate 2. The ability to use leaving groups as poor as hydroxyl or acyloxy allows utilization of substrates such as allyl alcohols or allyl carboxylates which are unreactive toward substitution until activated by the organometallic complex. At this point the original positional

identity of the leaving group is lost. For the substitution stage, the nucleophile normally attacks on the face of the allyl unit

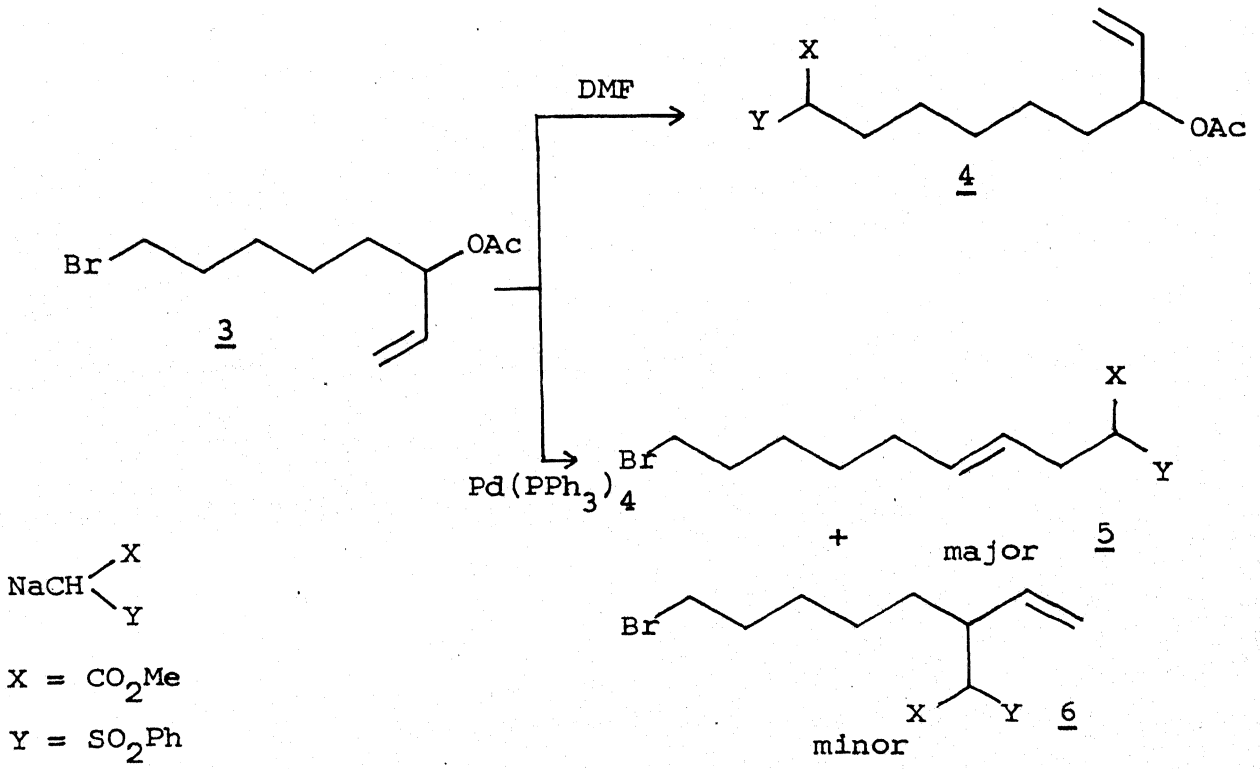


Scheme III.B.4

opposite to palladium. The inversion in the initial ionization and the inversion in the displacement lead to net retention in the substitution reaction. Attack of the nucleophile at C_a (Path A) or at C_b (Path B) depends upon the nature of the nucleophile, the nature of the substitution around the π-allyl unit and the nature

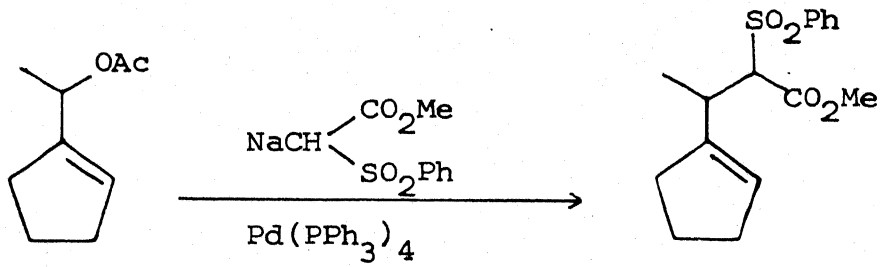
of the ligands on palladium. The attendant chemoselectivity regioselectivity and stereocontrol imparted by palladium (vide infra) offer an opportunity to change literally the roles of selectivity in organic synthesis.

Pd(0) catalyzed reactions have been found to be highly chemoselective. Thus, for example, the reaction of bromoacetate 3 with methyl benzenesulfonylacetate in hot dimethylformamide gave the acetate 4 as the sole product (Scheme III.B.5). However, in the presence of palladium, the activity was reversed and products derived from reaction at the allyl acetate were obtained exclusively.[3]



Scheme III.B.5

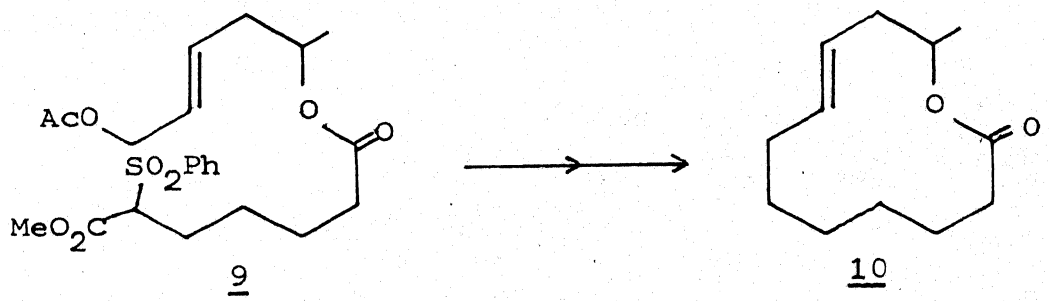
With substituted π-allylpalladium complexes the nucleophile may attack at either terminus to give linear and branched products (5 and 6 as shown in Scheme III.B.5). Attack at the less hindered site is fairly general and regioselectivity high. For example, alkylation of 1(1'-acetoxyethyl)cyclopentene (7) with benzenesulfonyl acetate gave exclusively 8 (Scheme III.B.6). Intramolecular reactions of π-allylpalladium complexes gave interesting



7 8

Scheme III.B.6

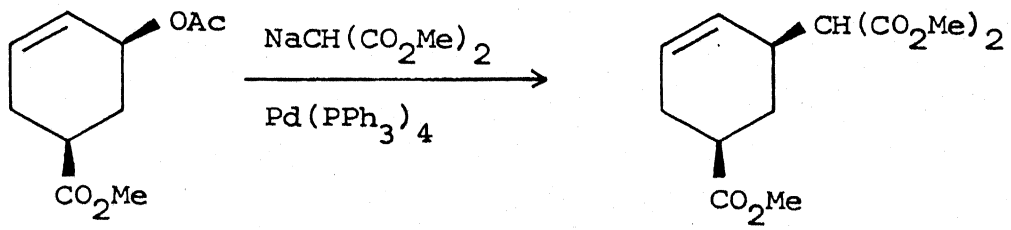
and unexpected results. For example, the synthesis of twelve membered lactone, reciteiolide (10) illustrates the regioselectivity of the Pd(0) catalyzed cyclization where the alkylation took place at the less substituted carbon atom [4] (Scheme III.B.7).



9 10

Scheme III.B.7

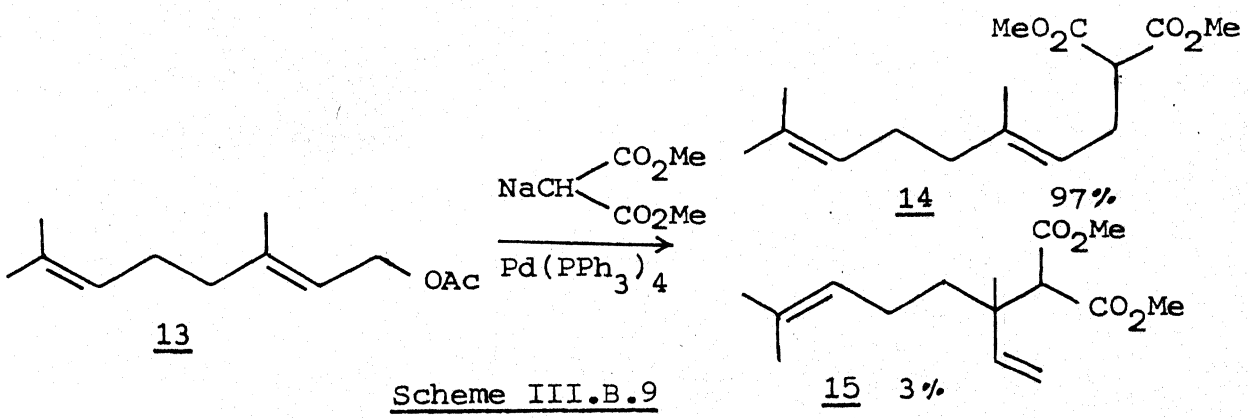
The stereochemical course of the Pd(0) catalyzed process has also been investigated both with respect to the carbon atom bearing the leaving group and the double bond. The alkylation of cis 3-acetoxy-5-methoxycarbonylcyclohexene (11) with dimethyl sodiomalonate led to a net S_N2 substitution with retention of configuration[5] (Scheme III.B.8). High degree of stereocontrol



11 12

Scheme III.B.8

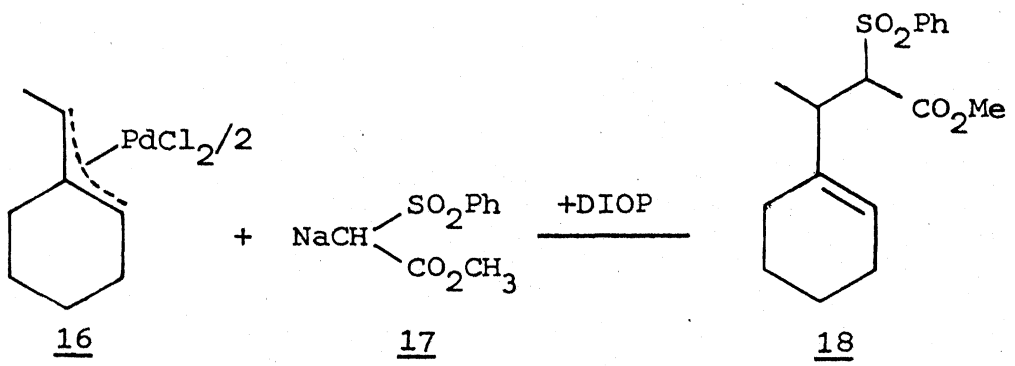
has been observed with respect to the geometry of the double bond. Thus for example, the reaction of trisubstituted allyl acetate 13 proceeded with retention of alkene stereochemistry with methyl benzenesulfonylacetate[3,5] (Scheme III.B.9).



13

Scheme III.B.9

Pd(0) catalyzed reactions have also been found to proceed with modest enantioselectivity in the presence of chiral phosphines.[6] For example, the reaction of 16 with 17 in the presence of trans-4,5-bis(diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolan (DIOP) gave 18 in 50-60 %e.e. (Scheme III.B.10).

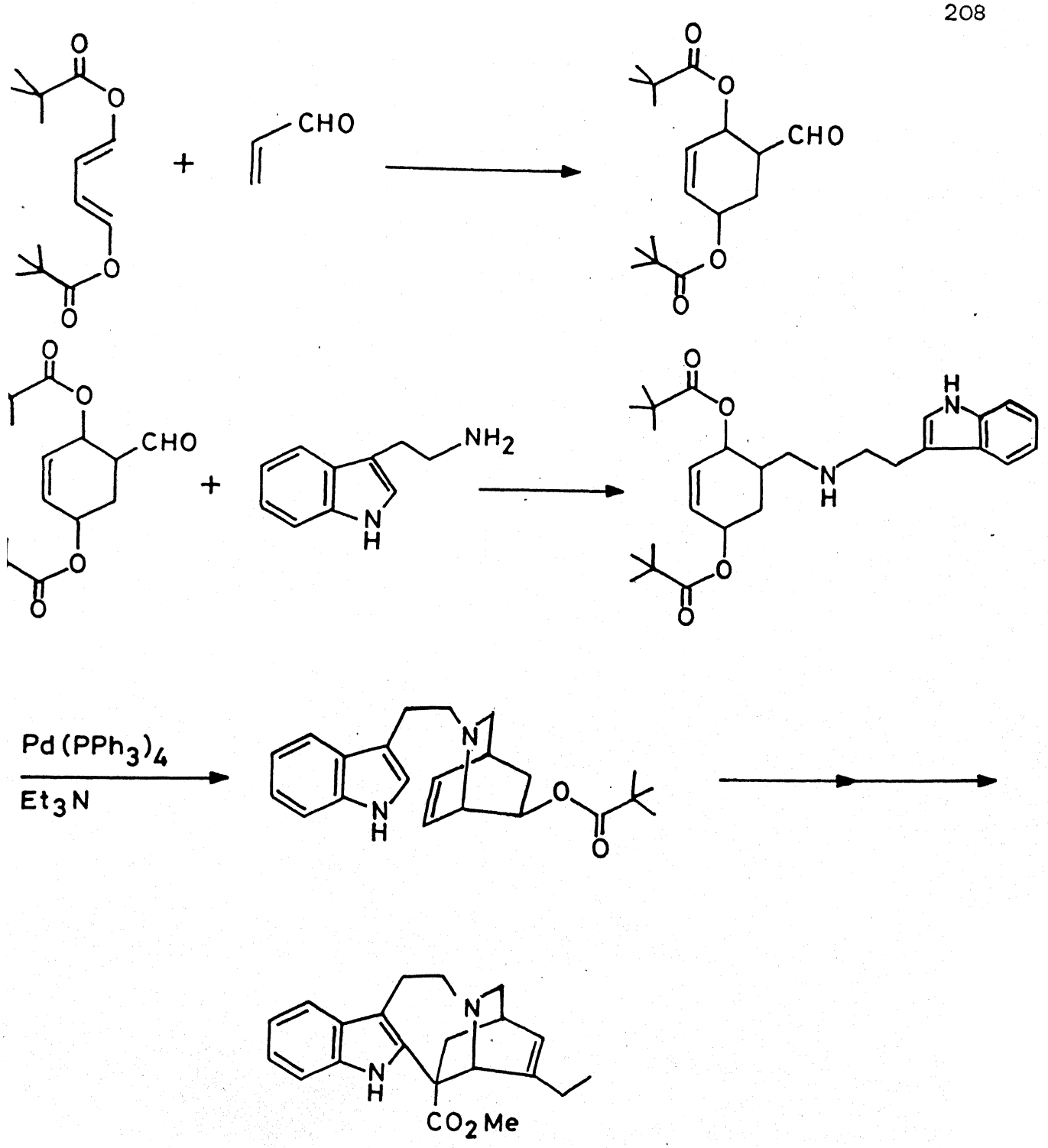


16 17 18

Scheme III.B.10

Not only carbon nucleophiles but nitrogen nucleophiles have also been used in the Pd(0) catalyzed alkylation reactions. For example, the use of nitrogen nucleophile in the synthesis of Catharanthine[7] (19) is shown in Scheme III.B.11.

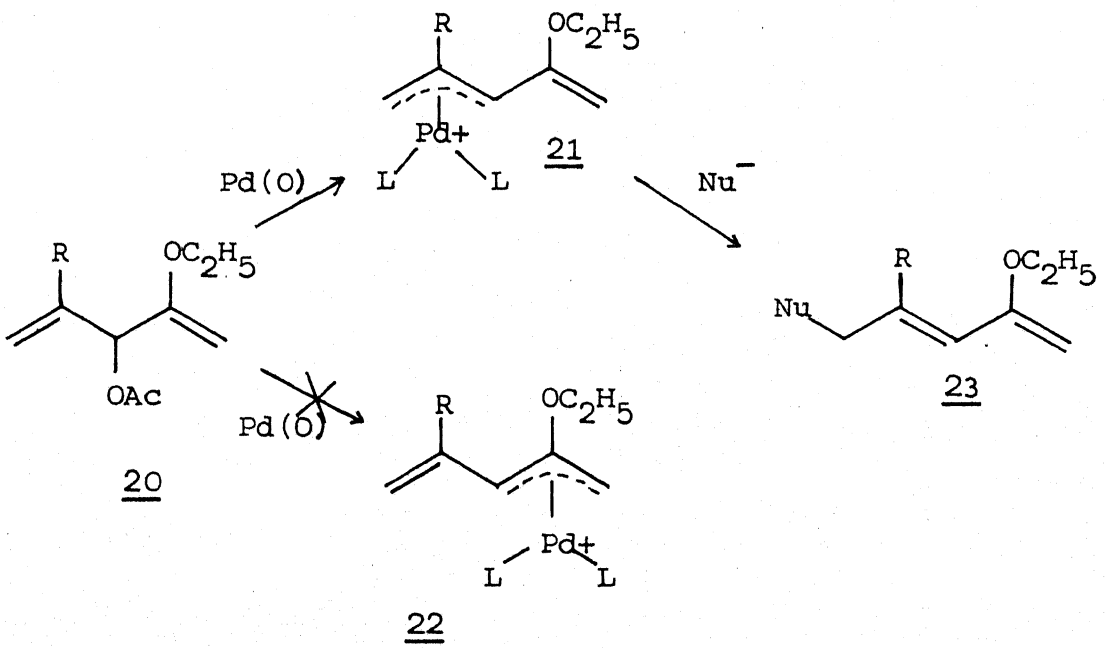
It is worthwhile to study the effect of substituents on the allyl acetate moiety, in particular on the vinyl carbon atom, in a Pd(0) catalyzed alkylation reaction. Trost et al.[8] have demonstrated the utility of 2-ethoxyallyl derivatives in such reactions. Ethoxy substituted allyl acetates were found to be less reactive compared to the simple alkyl substituted allyl acetates. Since the initiation of the process is believed to



19

Scheme III.B.11

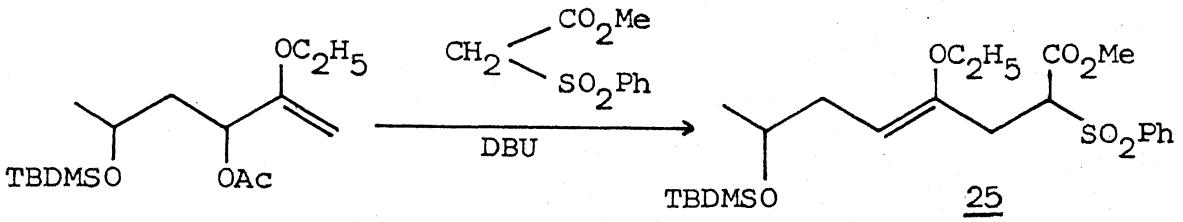
involve the formation of an olefin-palladium complex, such a first step would be destabilized by strong electron donating groups, such as ethoxy group. The effect of ethoxy substitution in the selective formation of π-allylpalladium complex is demonstrated in the example shown below. Thus, 20 was found to give only 21 and not 22 with Pd(0) as 22 further reacted with nucleophiles to give 23[8a] (Scheme III.B.12).



Scheme III.B.12

However, Pd(0) catalyzed reactions of 2-ethoxyallyl derivatives with nucleophiles have been found to proceed at higher temperatures. Ethoxy substituted allyl acetates exhibit a higher regioselectivity when compared with allyl acetates without the heteroatom substitution.[8a] Thus, for example 24 gave only one compound 25

where the nucleophile attacked at the terminal carbon atom only.

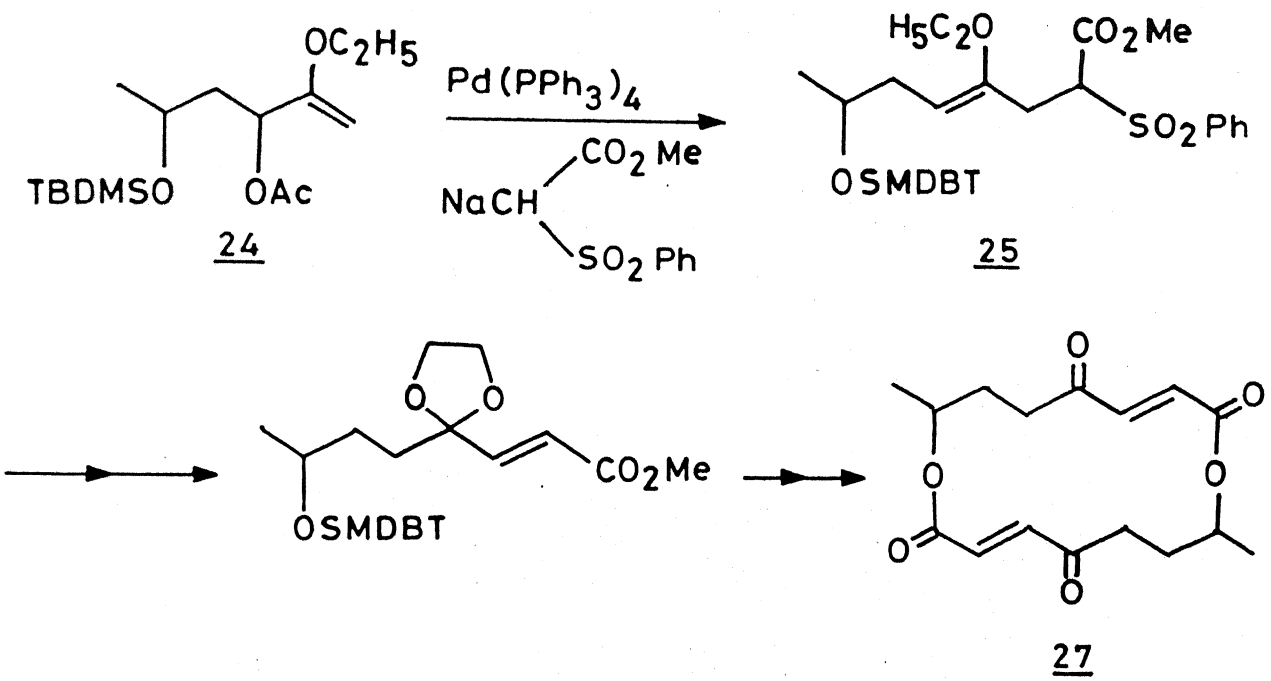


24 25

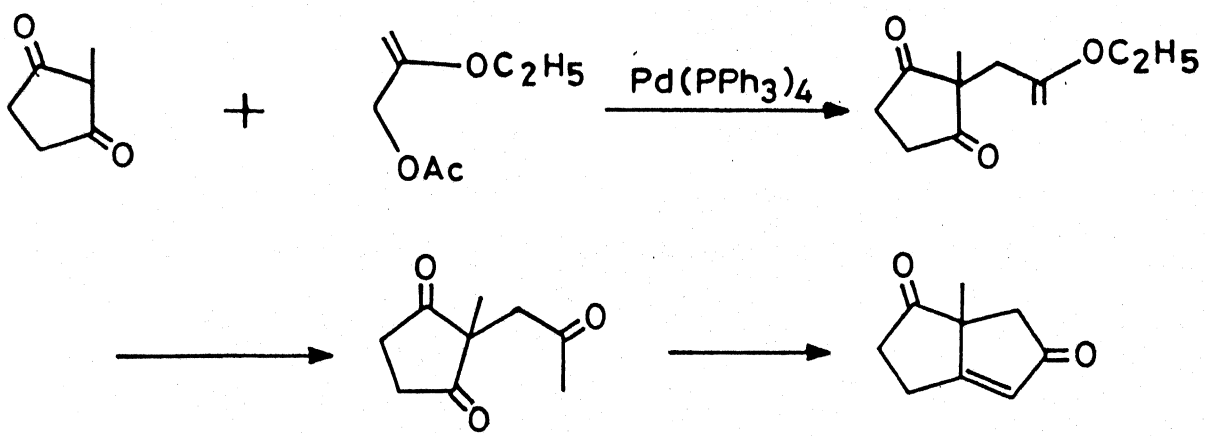
Further, ethoxy allyl acetate derivatives serve as the functional equivalent of an enolonium ion 26.

26

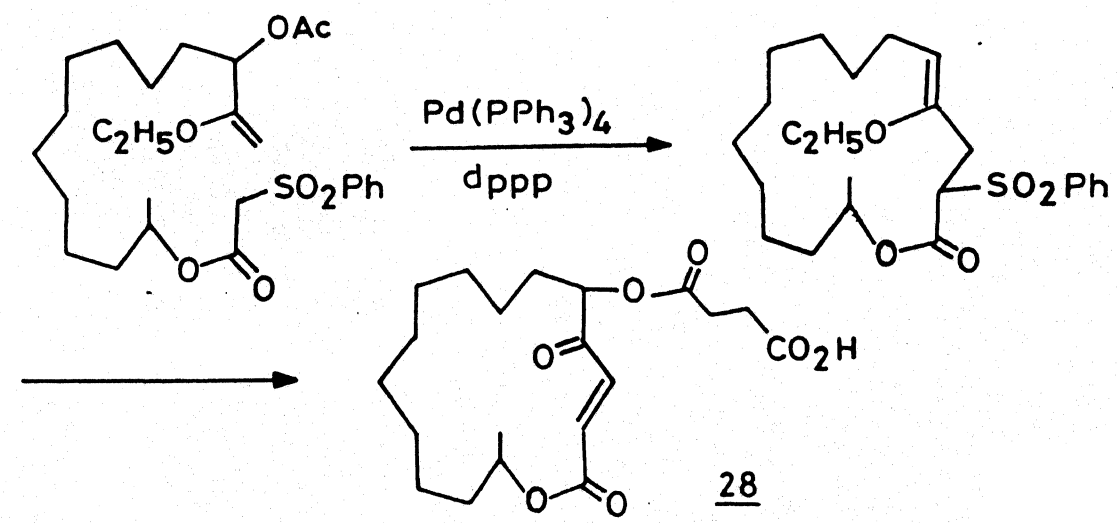
2-Ethoxyallyl derivatives have been employed in a formal total synthesis of ± pyrenophorin[8a] (27) (Scheme III.B.13), in cyclopentenone annulation[8b] (Scheme III.B.14) and in the synthesis of antibiotic A 26771 B (28)[8c] (Scheme III.B.15).



Scheme III.B.13



Scheme III.B.14

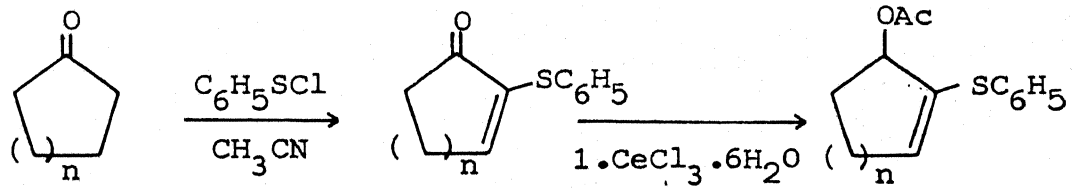


III.B.2 Results and Discussion

In the introduction part of this chapter it has been described that Pd(0) catalyzed reactions proceed in a highly chemo, regio and stereoselective manner. Further, substitution on the allyl acetate, for example with ethoxy group, exhibits a higher regioselectivity when compared with the alkyl substituted allyl acetates. π-Allylpalladium complex formation involves the initial coordination of the olefin with the catalyst. Such a process would be destabilized by strong electron donating group like ethoxy group on the allyl acetate. This was, infact, realized by Trost et al.[8] in their studies with ethoxy substituent. The reactions were found to be sluggish and required higher temperatures. On the other hand electron withdrawing groups would be expected to facilitate the formation of the initial complex.

The present study was undertaken to find out the effect of electron donating as well as the electron withdrawing substituents on the allyl acetate, in terms of reactivity and selectivity in a Pd(0) catalyzed reaction. Initial studies were carried out with the phenylthio substituent on the allyl acetate. Phenylthio group was chosen because of the following three reasons. (i) to compare the electron donating effect of 'S' vs 'O' (as reported with -OEt group), (ii) the vinyl sulphides are more stable than the vinyl ethers and (iii) vinyl sulphide functionality could be utilized for various transformations. Also, it was of interest to find out

the effect of sulphur poisoning of the Pd(0) catalyst. For these purposes two substrates viz. 1-acetoxy-2-phenylthiocyclopent-2-ene (30a) and 1-acetoxy-2-phenylthiocyclohex-2-ene (30b) were chosen. These substrates were prepared from the corresponding ketosulphides 29a,b which in turn prepared following the literature procedure[9] from the corresponding ketones using benzenesulfenyl chloride (Scheme III.B.16). These products 30a,b were characterized on the



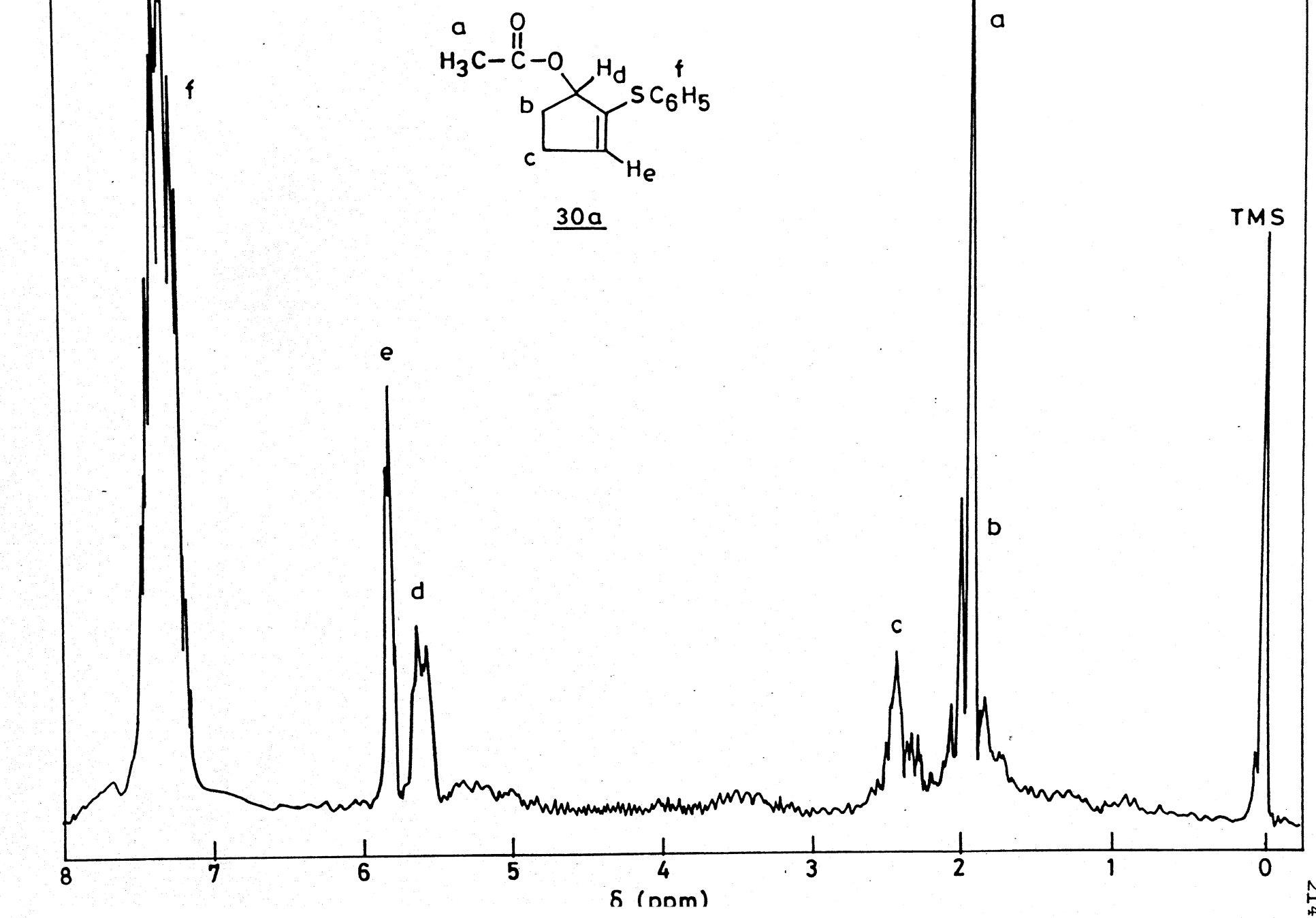
a n = 1

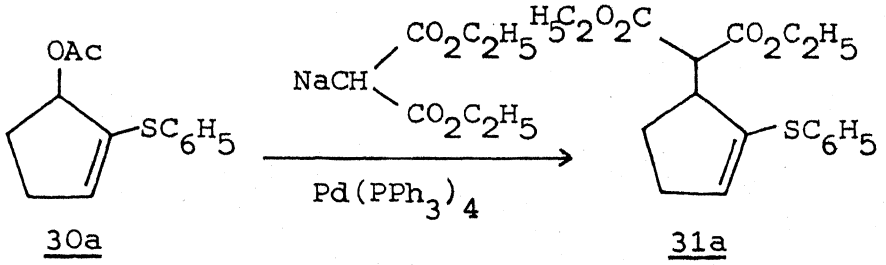
b n = 2

Scheme III.B.16

basis of spectral data (cf. experimental section). For example, ^{1}H NMR spectrum (Fig. III.B.1) of 30a showed absorptions at δ 1.9 (s, 3H, $COCH_3$), 1.78-2.12 (m, 2H, CH_2), 2.25-2.62 (m, 2H, allylic CH_2), 5.6 (m, 1H, CH-OAc), 5.8 (t, 1H, J=3 Hz, vinylic), 7.3 (m, 5H, aromatic).

The reaction of 30a with diethyl sodiomalonate and catalytic amount of $Pd(PPh_3)_4$ in DMSO at room temperature for 30 h gave 31a in 66 % yield (Scheme III.B.17). Its IR spectrum showed absorption at 1730 ($\nu_{C=O}$) cm^{-1} and its ^{1}H NMR spectrum (Fig. III.B.2) showed


a
O
H3C–C–O
Hd
f
SC6H5
b
c
He
30a
f
e
d
c
b
a
TMS
8
7
6
5
4
3
2
1
0
δ (ppm)



30a 31a

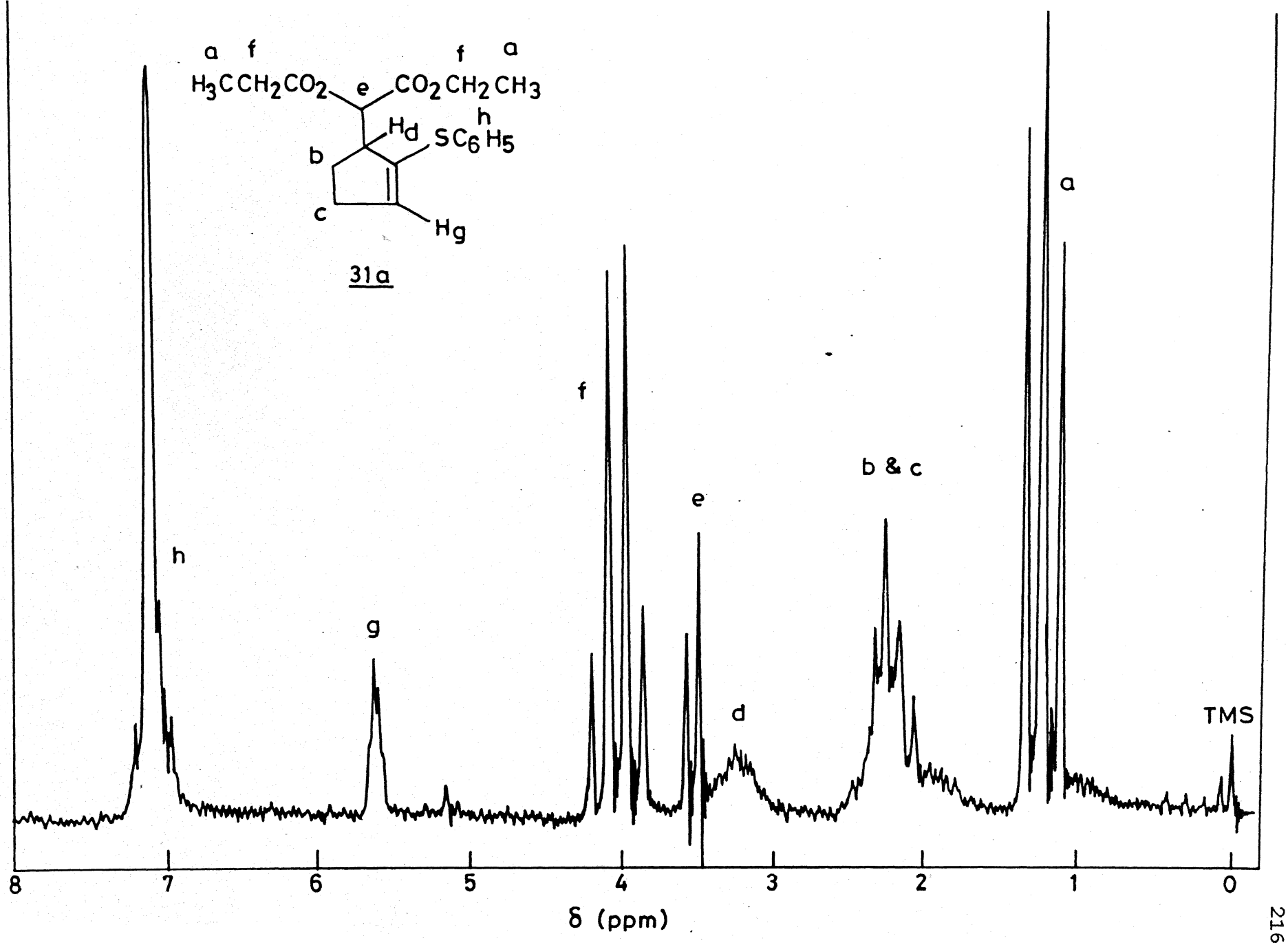
Scheme III.B.17

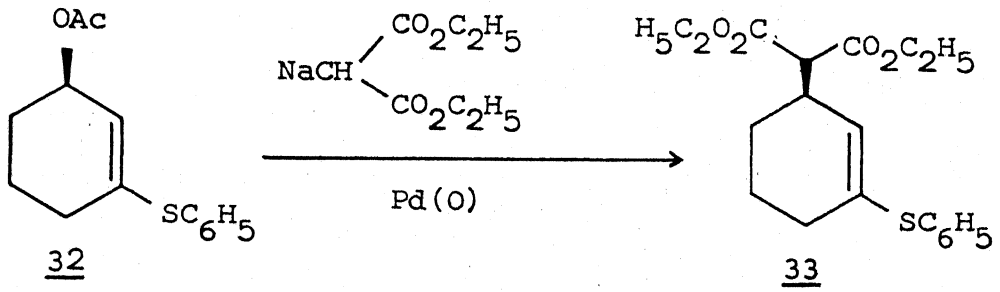
absorptions at δ 1.2 (t, J=7 Hz, 6H, CH_3), 2.0–2.43 (m, 2H, allylic CH_2), 3.0–3.4 (m, 1H, allylic CH), 3.53 (d, J=5 Hz, 1H, $\underline{H}C(CO_2C_2H_5)_2$), 4.03 (q, J=7 Hz, 4H, $COC\underline{H}_2$), 5.6 (m, 1H, vinylic) and at 7.1 (m, 5H, aromatic). Further its mass spectrum showed a molecular ion peak at 334. These data confirm the structure assigned to 30a.

In a similar fashion, the reaction of 30b with diethyl sodiomalonate at room temperature for 36 h gave 31b in 73% yield. The structure was assigned on the basis of spectral and analytical data (cf. experimental section).

The above two reactions were cleaner and proceeded under mild reaction conditions (i.e. at room temperature) compared to the ethoxy substituted reactions as reported by Trost et al.[8] This clearly indicates that phenylthio group is a better alternative to ethoxy group. Moreover, it is interesting to note that, there is no sulphur poisoning under the experimental conditions.

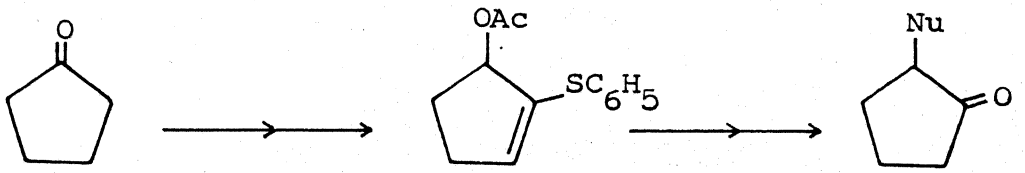
While our work was being carried out, Godleski et al.[10] reported a palladium mediated reaction with phenylthio substitution at the terminal carbon atom of the allyl acetate, such as 32. This substitution is at a different carbon atom compared to the cases studied by us. Thus, the reaction of 32 with diethyl sodiomalonate gave 33 with a net retention of configuration.


a f
H3CCH2CO2
e
CO2CH2CH3
f a
h
Hd
SC6H5
b
c
Hg
31a
h
g
f
e
d
b & c
a
TMS
8
7
6
5
4
3
2
1
0
δ (ppm)



32 33

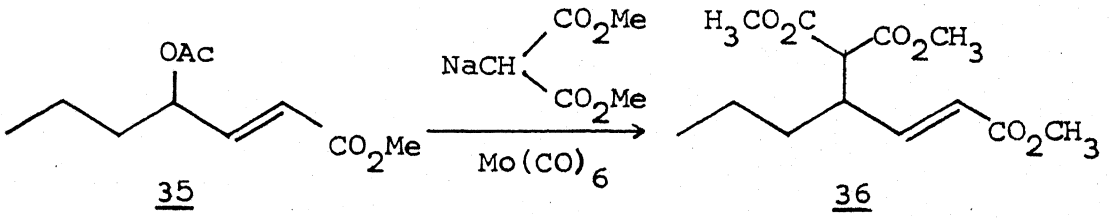
Further, the results of our investigation provide a convenient method for the preparation of substrates like 34 starting from the corresponding ketones.



34

Nu = nucleophile

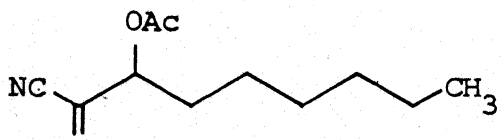
It was of interest to study the effect of electron withdrawing groups on the allyl acetate in a Pd(0) catalyzed reaction, because such groups would be expected to facilitate the coordination of olefins with the catalyst. No study has been reported in the literature with electron withdrawing groups on the vinyl carbon of the allyl acetate in a Pd(0) catalyzed alkylation reactions. However, recently Trost et al.[11] have reported such reactions with Mo catalyst. For example, the reaction of 35 with dimethyl sodiomalonate in the presence of Mo catalyst gave 36. This reaction proceeds via π-allylmolybdenum complex (Scheme III.B.18).



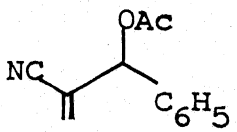
35 36

Scheme III.B.18

We were interested in studying the effect of cyano group which is moderately electron withdrawing, on the vinyl carbon of the allyl acetate. Two substrates viz. 37a,b were chosen for the present study. These substrates were prepared following the literature procedure[12] and characterized on the basis of spectral



37a



37b

data (cf. experimental section). For example, ^{1}H NMR spectrum (Fig. III.B.3) of 37a showed absorptions at δ 0.85 (t, 3H, J=6 Hz, CH_3), 1.18-1.56 (m, 8H, CH_2), 1.56-2 (m, 2H, CH_2), 2.05 (s, 3H, $COCH_3$), 5.2 (t, 1H, J=7 Hz, CH-OAc), 5.93 and 6.0 (2s, 2H, vinylic).

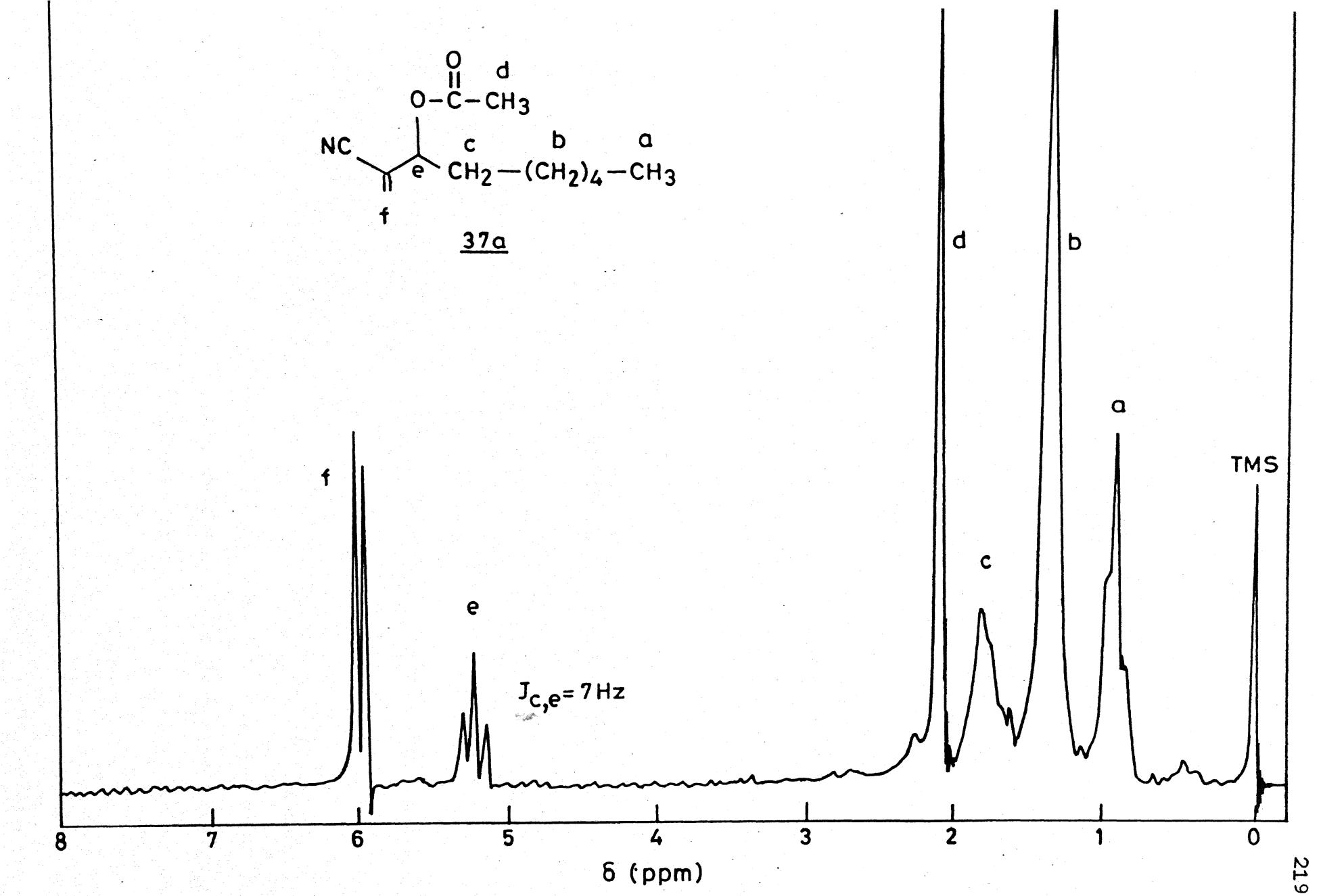
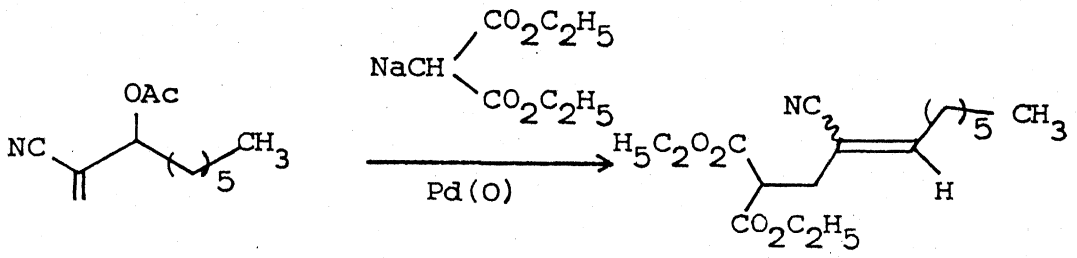


Fig. III.B.3 ^{1}H NMR spectrum (90 MHz) of 37a.

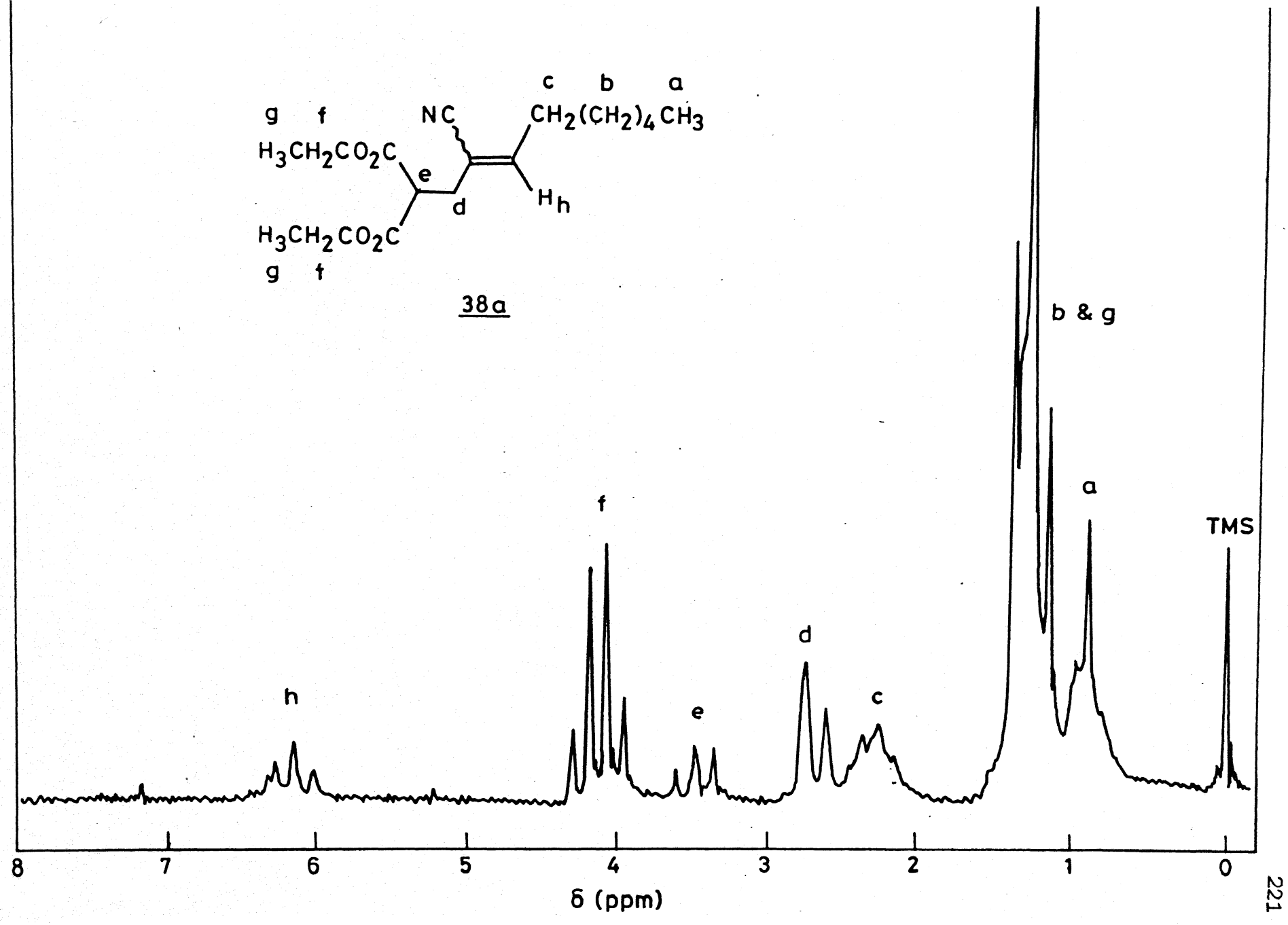
Reaction of 37a with diethyl sodiomalonate in the presence of Pd(0) in DMSO at room temperature for 10 h gave 38a (Scheme III.B.19). Its IR spectrum showed absorptions at 2220 ($\nu_{C\ N}$) and



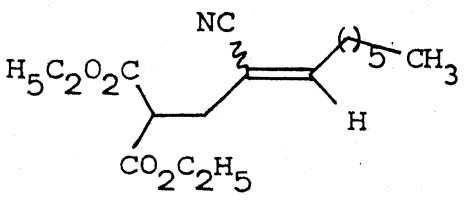
37a 38a

Scheme III.B.19

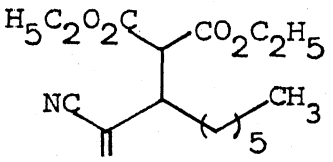
at 1735 ($\nu_{C=O}$) cm^{-1} and its ^1H NMR spectrum (Fig. III.B.4) showed absorptions at δ 1.06-1.63 (m, 14H, CH_2 and CH_3), 0.93 (t, 3H, CH_3), 2.0-2.56(m, 2H, allylic CH_2), 2.7 (d, 2H, J=7.5 Hz, allylic CH_2), 3.5 (t, 1H, J=7.5 Hz, $\underline{H}C(CO_2C_2H_5)_2$), 4.16 (q, 4H, $COCH_2$), 6.0-6.36 (m, 1H, vinylic). Further its mass spectrum showed a molecular ion peak at 309. These data confirm the structure assigned to 38a. Although it was difficult to assess the stereochemistry of the olefin from the olefinic pattern in the ^1H NMR spectrum, it appears to be a single stereoisomer. Had it been a mixture of two isomers, then ^1H NMR spectrum should have shown two multiplets for the vinylic protons at two different chemical shifts. From


c b a
g f
NC
CH2(CH2)4CH3
H3CH2CO2C
e
d
Hh
H3CH2CO2C
g f
38a
b & g
a
TMS
f
d
h
e
c
8
7
6
5
4
3
2
1
0
δ (ppm)

the olefinic pattern of the ^1H NMR spectrum of 38a it was also evident that it is not a terminal olefin i.e. 39a but it is an internal olefin 38a (cf. Fig. III.B.4). Thus, the reaction



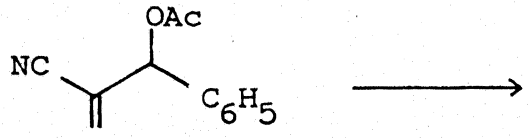
38a



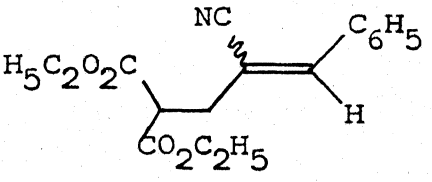
39a

proceeded in a highly regio and stereoselective manner where the nucleophile attacked at the less hindered terminal olefinic carbon atom.

In a similar fashion, reaction of 37b with diethyl sodiomalonate gave 38b in 90% yield. The structure of 38b was confirmed



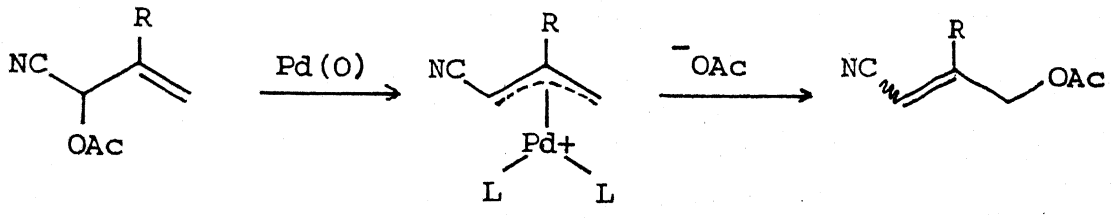
37b



38b

on the basis of spectral and analytical data (cf. experimental section). Spectral data also confirm that it is a single compound.

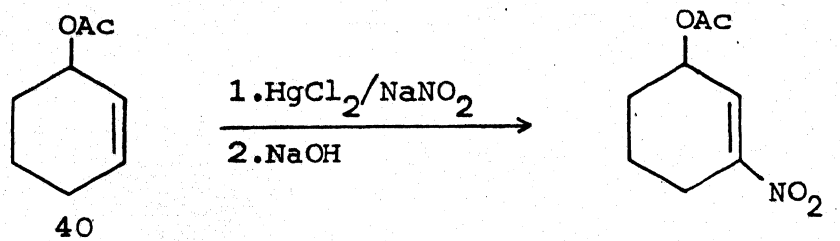
The above reactions are expected to have proceeded via π-allylpalladium complex. Formation of π-allylpalladium complex from allyl acetate with a cyano substitution has a precedent in the literature. Mandai et al.[13] reported allylic rearrangement of cyano allyl acetate using Pd(0) (Scheme III.B.20).



Scheme III.B.20

Thus, the Pd(0) catalyzed allylic functionalization of cyano substituted allyl acetates proceeded under mild reaction conditions and with high degree of regio and stereoselectivity.

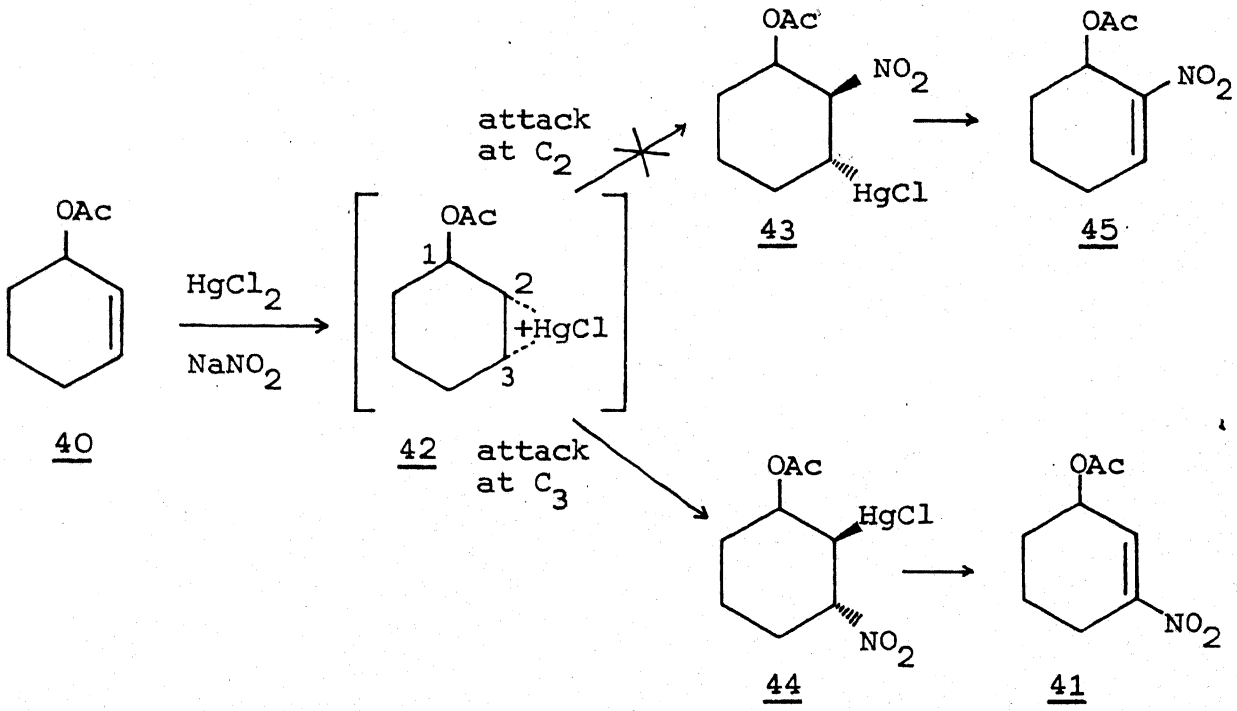
In the present study, the effect of nitro substituent on the allyl acetate in a Pd(0) catalyzed reaction has also been included. For this purpose, 1-acetoxy-3-nitrocyclohex-2-ene (41) was prepared, for the first time, starting from 1-acetoxy-2-cyclohexene (40), adapting Corey's nitromercuration chemistry.[14] Treatment of 40 with mercuric chloride-sodium nitrite followed by sodium hydroxide gave 41 in 53 % yield. Compound 41 was characterized on



40 41

the basis of spectral and analytical data (cf. experimental section) Thus, for example, ^{1}H NMR spectrum of 41 showed absorptions at δ 1.86 (m, 4H, CH_2), 2.05 (s, 3H, $COCH_3$), 2.65(m, 2H, allylic CH_2),

5.5 (m, 1H, CH-OAc), 7.1 (d, 1H, J=3 Hz, vinylic). The regioselectivity in the reaction is expected due to steric interference of the acetoxy group towards the attack of NO_2^- on the complex 42 (Scheme III.B.21). The other product 45 does not seem to have



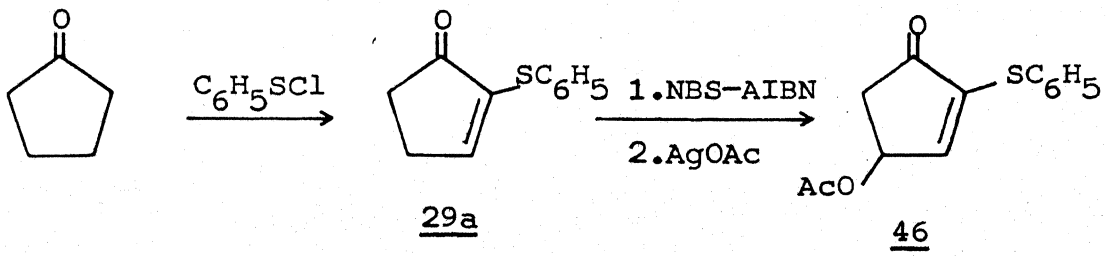
Scheme III.B.21

formed as the ^1H NMR spectrum clearly shows a doublet at δ 7.1 for the vinylic proton which is only possible with compound 41 and not 45.

Reaction of this substrate 41 under a variety of experimental conditions, with diethyl sodiomalonate in the presence of Pd(0) gave a number of products from which isolation of any product in pure form became difficult. Then, a blank reaction with diethyl

sodiomalonate was tried and it also found to give a number of products. Under the present reaction conditions, it is clear that the reaction is not selective.

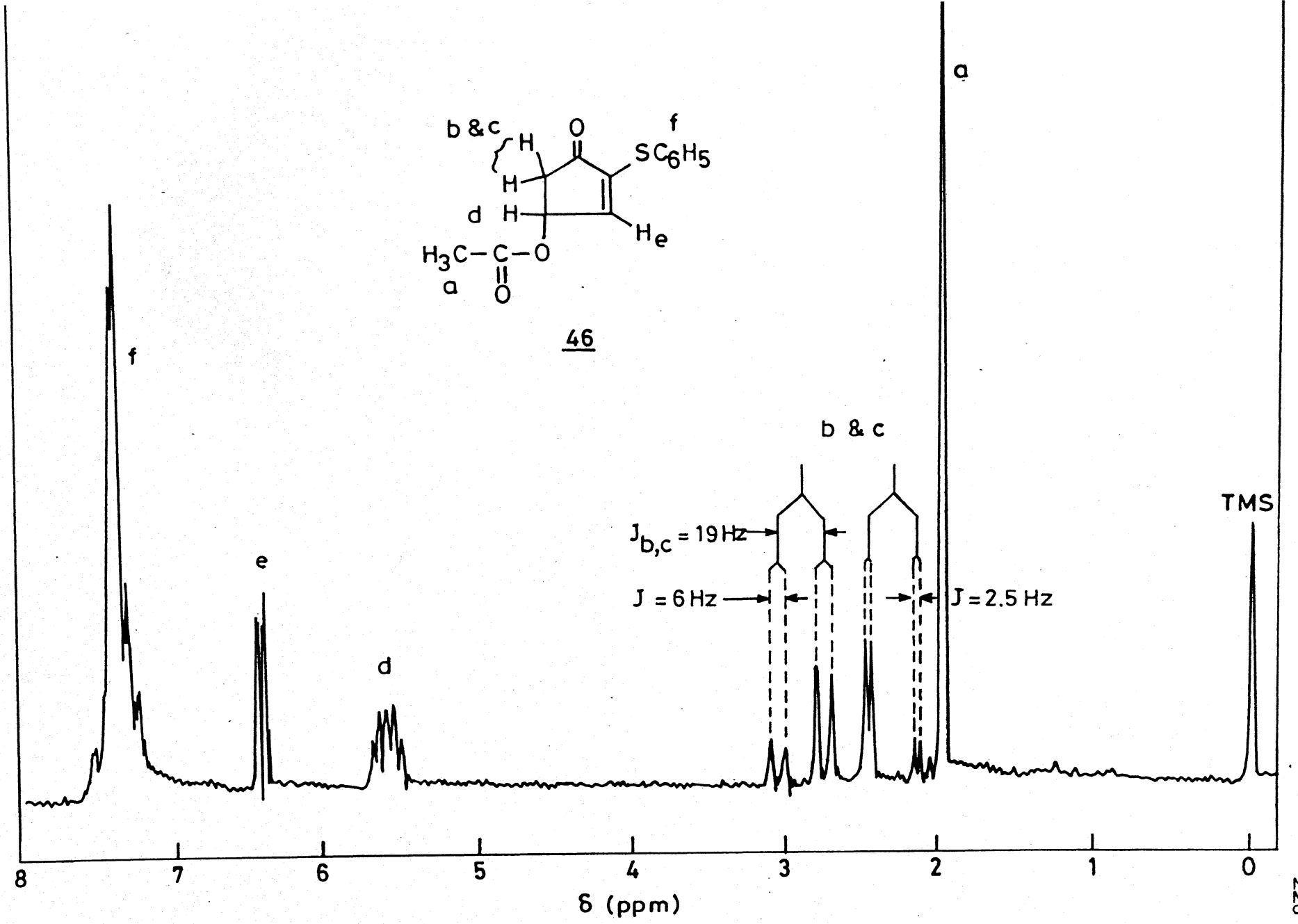
It was also of interest to study the effect of other functional groups in the vicinity of the substituted allyl acetates in a Pd(0) catalyzed alkylation reaction. Substrate 46 was chosen for this purpose. It was synthesized for the first time, from keto-sulphide 29a in 54% yield. The structure was assigned on the basis



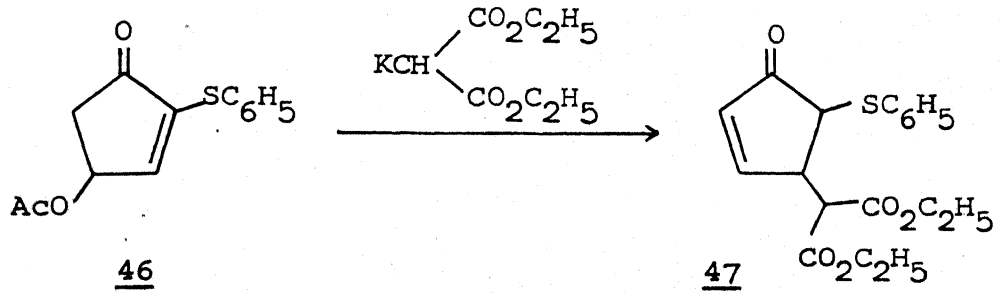
29a 46

of spectral and analytical data. Thus, its IR spectrum showed absorptions at 1740 cm^{-1} and at 1720 cm^{-1} indicating the presence of both an ester and a conjugated enone functionalities and its ^1H NMR spectrum (Fig. III.B.5) showed absorptions at δ 2.0 (s, 3H, $COCH_3$), 2.33 (dd, gem H, J=19 Hz, 2.5 Hz), 2.93 (dd, gem H, J=19 Hz, 6 Hz), 5.63 (m, 1H, CH-OAc), 6.46 (d, 1H, J=3 Hz, vinylic), 7.33 (m, 5H, aromatic). Further its mass spectrum indicated a molecular ion peak at 248.

Reaction of 46 with diethyl sodiomalonate in the presence of Pd(0) catalyst, under a variety of experimental conditions, gave a number of products. Isolation of any useful product from the


b & c
f
SC6H5
H
H
d H
He
H3C–C–O
a
O
46
a
f
e
d
b & c
TMS
Jb,c = 19 Hz
J = 6 Hz
J = 2.5 Hz
8
7
6
5
4
3
2
1
0
δ (ppm)

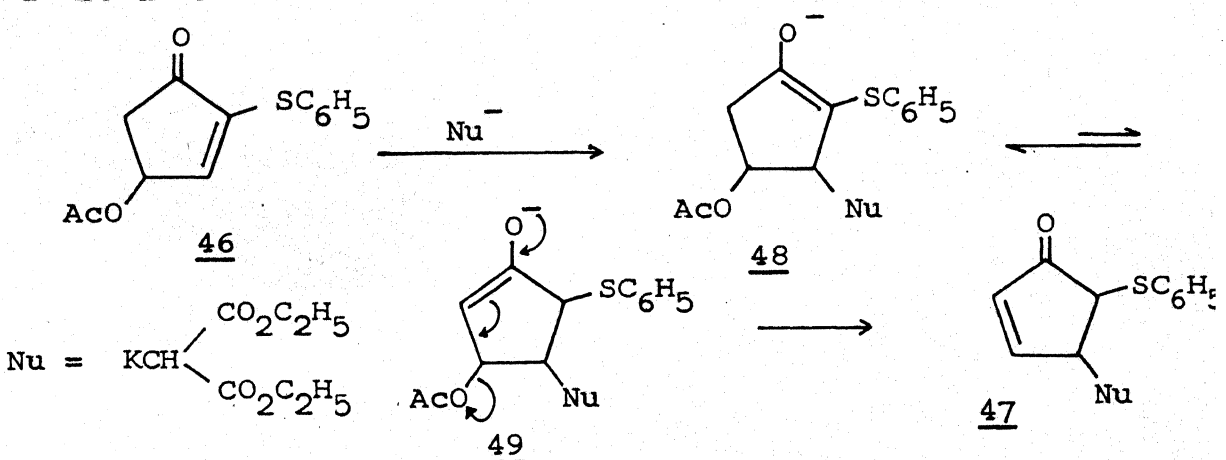
mixture became difficult. Then, a blank reaction was tried with diethyl potassiomalonate in glyme. The reaction gave a very interesting compound 47 in 51% yield. IR spectrum of this



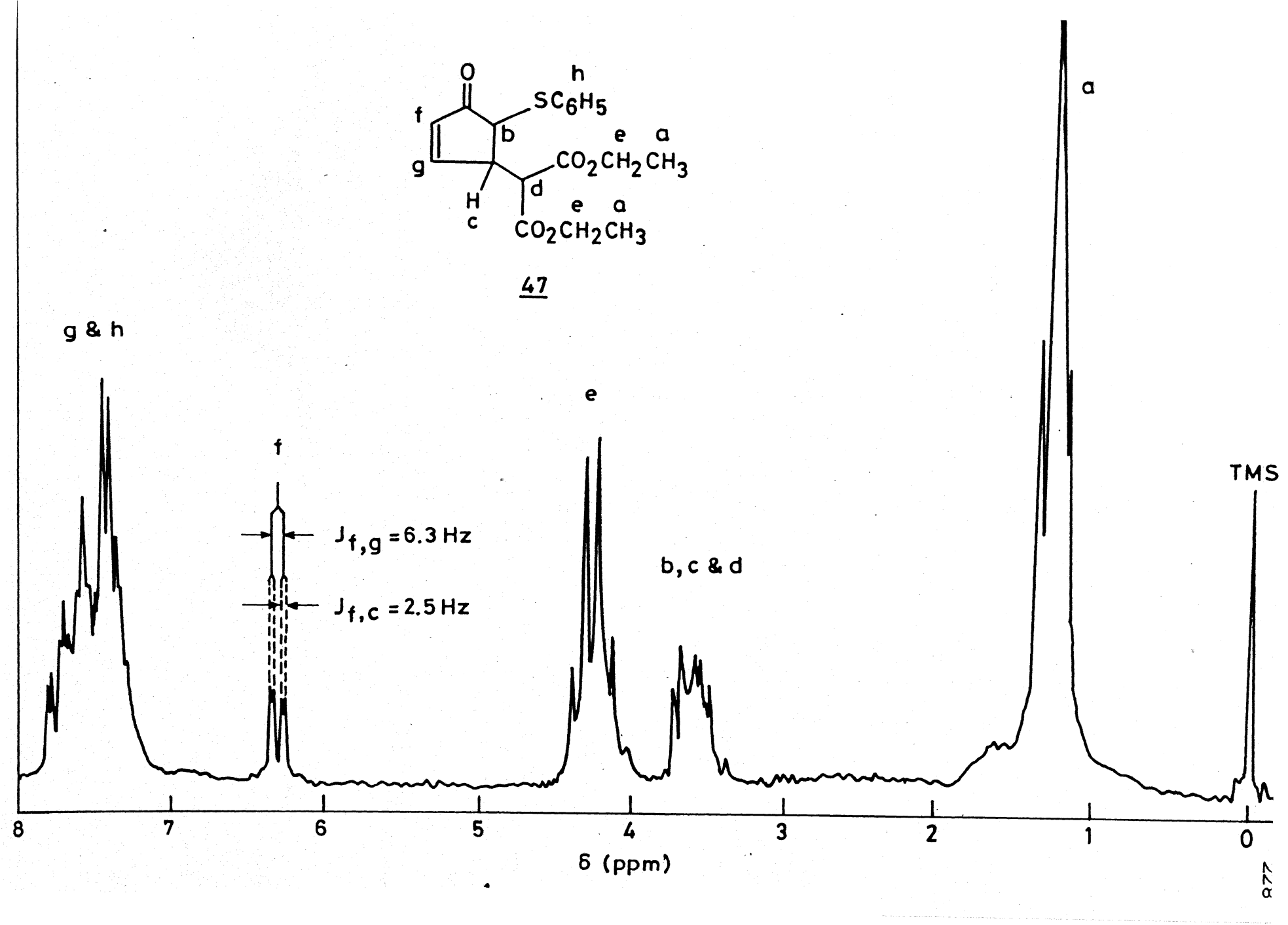
46 47

compound showed a broad absorption at 1730 cm^{-1}. Its ^1H NMR (Fig. III.B.6) spectrum showed absorptions at δ 1.28 (t, 6H, CH_3), 3.44-3.78 (m, 3H, C<u>H</u>-SC_6H_5, C<u>H</u>$(CO_2C_2H_5)_2$ and allylic CH), 4.31 (q, 4H, CH_2), 6.31 (dd, J=6.2 Hz, 2.5 Hz, 1H, COC<u>H</u>), 7.46-7.84 (m, 6H, aromatic and COCH=C<u>H</u>). Mass spectrum showed a molecular ion peak at 348. These data confirm the structure assigned to 42.

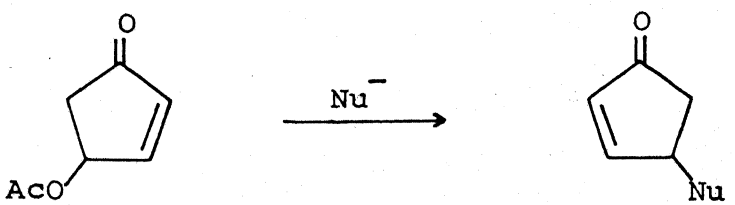
Formation of the product 47 could be explained on the basis of a mechanism shown below.



Scheme III.B.22


O
h
SC6H5
f
b
e a
g
CO2CH2CH3
d
H
c
e a
CO2CH2CH3
47
g & h
f
e
a
TMS
b, c & d
Jf,g = 6.3 Hz
Jf,c = 2.5 Hz
8
7
6
5
4
3
2
1
0
δ (ppm)

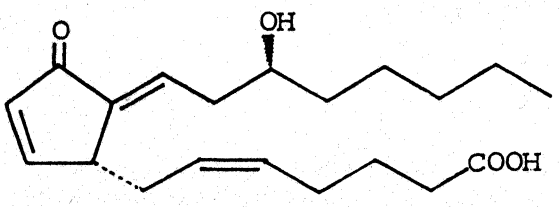
Addition of diethyl sodiomalonate could give the enolate ion 48 which could be in equilibrium with 49. Elimination of acetate ion from 49 could give the product 47. Winterfeldt et al.[15] have reported earlier a similar kind of rearrangement on 4-acetoxy-2-cyclopentenone 50 with various nucleophiles.



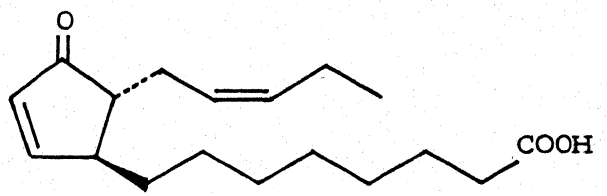
50 51

Nu = nucleophile

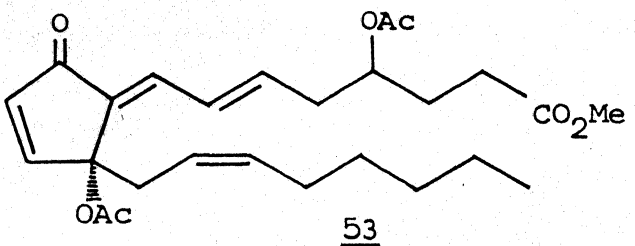
The above mentioned reaction i.e. the conversion of 4-acetoxy-2-phenylthiocyclopent-2-enone (46) to 47 is of particular interest to us because this methodology could be adapted for a simple synthesis of prostaglandin D_2 metabolite[16a] viz. 9-deoxy-Δ^9, Δ^{12}-13,14-dihydro PGD_2 (52) which has close structure resemblance with Clavulones[16b] 53 and also for the synthesis of Dicranenones 54.[16c]



52

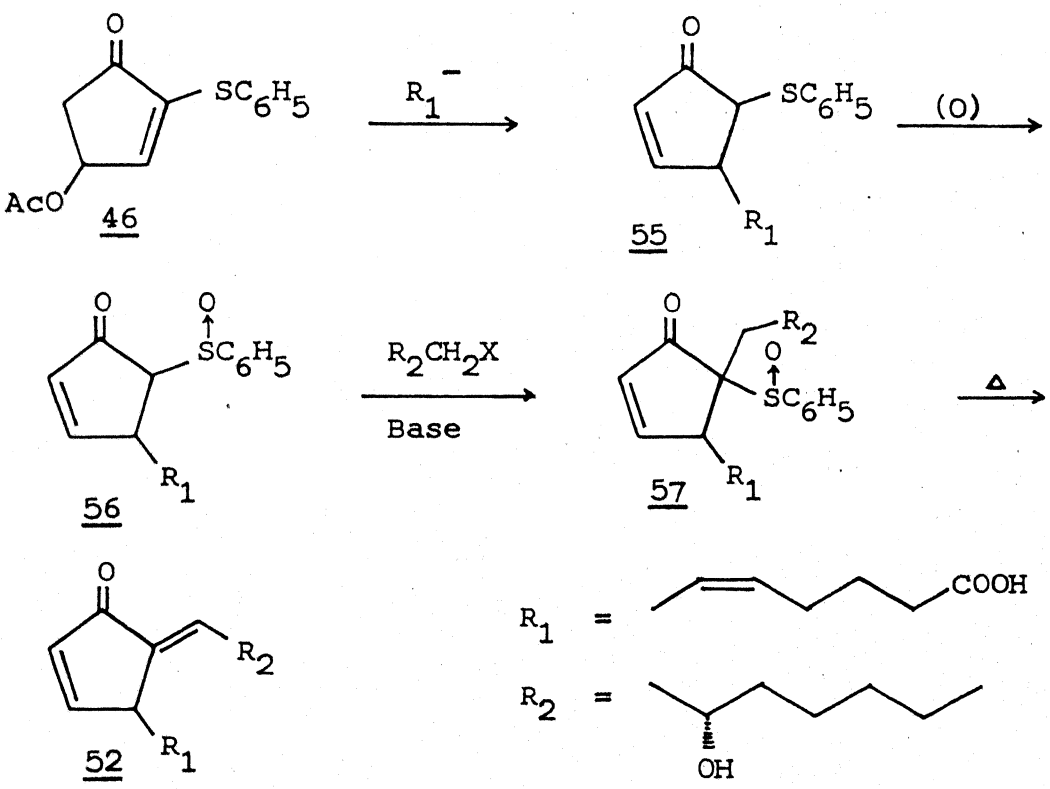


54



53

It is expected that oxidation of 55 to get 56, which on alkylation followed by elimination of sulphoxide would give the PGD_2 metabolite 52 (Scheme III.B.23).



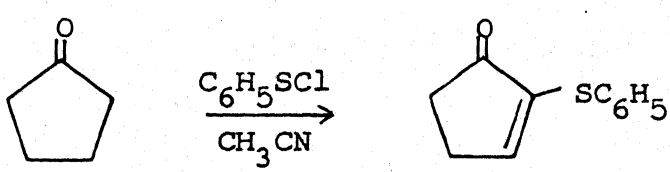
Scheme III.B.23

Thus, the present study clearly indicates that Pd(O) catalyzed allylic alkylation of phenylthio and cyano substituted allyl acetates proceed under mild reaction conditions and with cyano group high degree of regio and stereoselectivity is obtained.

III.B.3 Experimental

The details of the instruments used are the same as described in section I.3. The solvents used were dried in the same manner as described in Sections I.3 and II.3. Benzenesulfenyl chloride was prepared from diphenyl disulphide and sulfuryl chloride following the literature procedure.[18] Tetrakis(triphenylphosphine)palladium(0) was prepared from $PdCl_2$ following the literature procedure.[19]

Preparation of 2-phenylthiocyclopent-2-enone (29a)



29a

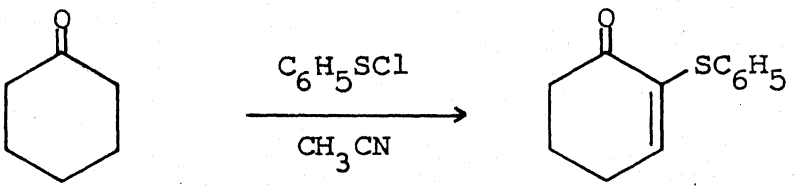
Benzenesulfenyl chloride (15.7 g, 0.11 mol) was added to a solution of cyclopentanone (3 g, 0.036 mol) in dry CH_3CN (50 mL) at 15-20°C during 30 min. Then it was allowed to stir at room temperature for 2 h. After cooling in an ice-water bath, the solid diphenyl disulphide was filtered and washed with cold acetonitrile. The filtrate was evaporated under reduced pressure. To the residue, boiled methanol (50 mL) was added and the mixture reevaporated under vacuum and the whole process repeated for a second time. Chromatography of the oily residue on a silica gel

column [eluent, pet. ether:ether (60:40)] gave 2-phenylthiocyclopent-2-enone(29a). It was further recrystallized from pet.ether. Yield, 3.2 g (47%), m.p. 60-62°C (lit[17], m.p. 64-65°C).

IR spectrum $\nu_{max}(CHCl_3)$: 1700 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 2.32-2.7 (m, 4H, CH_2), 6.75-6.9 (t, J=3 Hz, 1H, olefinic), 7.2-7.5 (m, 5H, aromatic).

Preparation of 2-phenylthiocyclohex-2-enone (29b)



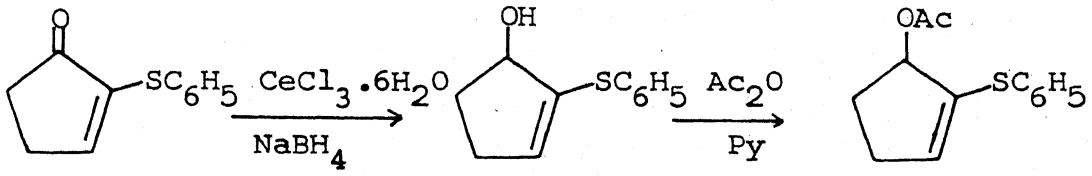
29b

Following the above described procedure for 29a, the reaction of cyclohexanone (490 mg, 5 mmol) and benzenesulfenyl chloride (2.2 g, 15.3 mmol) for 2 h at room temperature gave crude 29b which was purified by column chromatography [eluent, pet.ether: ether (60:40)]. Yield, 600 mg (58%).

IR spectrum ν_{max}(neat): 1670 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 6.51 (t, J=4.5 Hz, 1H, olefinic).

Preparation of 1-acetoxy-2-phenylthiocyclopent-2-ene (30a)



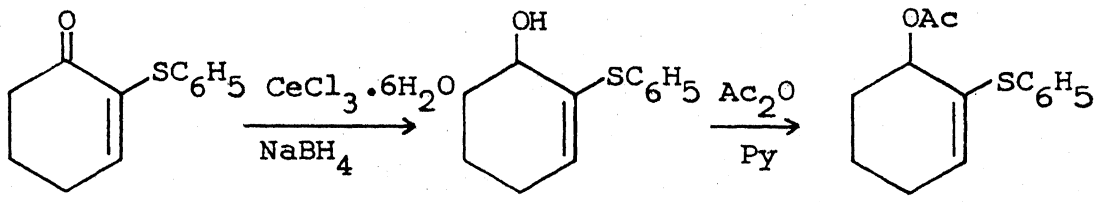
29a 30a

2-Phenylthiocyclopent-2-enone (29a) (500 mg, 2.63 mmol) and $CeCl_3.6H_2O$ (935 mg, 2.63 mmol) were dissolved in MeOH (6.5 mL). Sodium borohydride(100 mg, 2.63 mmol) was added in one portion, and stirred for 5 min. MeOH was removed under reduced pressure, the residue was dissolved in ether (25 mL) and neutralized with satd. aq. NH_4Cl. The organic layer was separated and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude product which was acetylated using acetic anhydride (0.5 mL, 5.26 mmol) and pyridine (0.85 mL, 10.5 mmol) in CH_2Cl_2 at room temperature for 12 h. The crude acetate was purified by column chromatography [eluent, pet.ether:ether (80:20)] to obtain 30a as a thick liquid. Yield, 520 mg (84%).

IR spectrum ν_{max}(neat): 1725 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.9 (s, 3H, $COCH_3$), 1.78-2.12 (m, 2H, CH_2), 2.25-2.62 (m, 2H, allylic CH_2), 5.6 (m, 1H, C<u>H</u>-OAc), 5.8 (t, 1H, J=3 Hz, vinylic), 7.3 (m, 5H, aromatic).

Preparation of 1-acetoxy-2-phenylthiocyclohex-2-ene (30b)



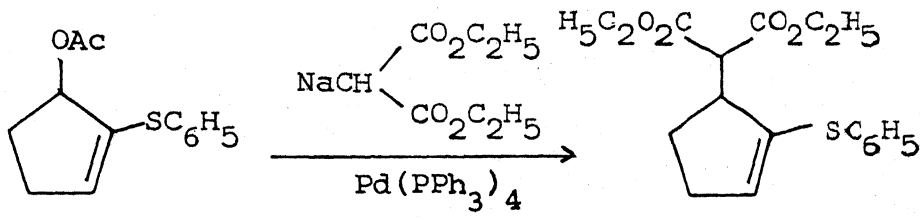
29b 30b

The reaction was carried out following the above described procedure. The reaction of 2-phenylthiocyclohex-2-enone 29b (204 mg, 1 mmol) with $NaBH_4$ (38 mg, 1 mmol) in the presence of $CeCl_3 \cdot 6H_2O$ (355 mg, 1 mmol) in MeOH (2.5 mL) at room temperature for 5 min. gave a crude alcohol which was acetylated using acetic anhydride (0.2 mL, 2.12 mmol) and pyridine (0.32 mL, 4 mmol) in CH_2Cl_2 (3 mL) for 12 h. at room temperature. The crude acetate was purified by column chromatography [eluent, pet.ether:ether (80:20)] to obtain 30b as a thick oil. Yield, 195 mg (79%).

IR spectrum ν_{max}(neat): 1725 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.75 (m, 4H, sat CH_2), 2.16 (m, 2H, allylic CH_2), 5.31 (m, 1H, C<u>H</u>-OAc), 6.34 (t, 1H, J=3.7 Hz, vinylic), 7.34 (m, 5H, aromatic).

Preparation of 3-(αα-dicarboethoxy methyl)-2-phenylthiocyclopentene (31a)



30a 31a

1-Acetoxy-2-phenylthiocyclopent-2-ene (30a) (234 mg, 1 mmol) in DMSO (0.5 mL) was added to a mixture of diethyl sodiomalonate [prepared from diethyl malonate (560 mg, 3.5 mmol) and NaH (175 mg, 3.5 mmol), 50% dispersion in oil)], triphenylphosphine (78 mg, 0.3 mmol) and tetrakis(triphenylphosphine)palladium(O) (12 mg, 0.01 mmol) in DMSO (5 mL) at room temperature under nitrogen atmosphere. Then, the resultant mixture was stirred for additional 30 h at room temperature. Addition of water(5 mL) followed by extraction with ether (3 x15 mL) gave a crude product. It was purified by column chromatography [eluent, pet.ether:ether (80:20)]. Yield, 220 mg (66%).

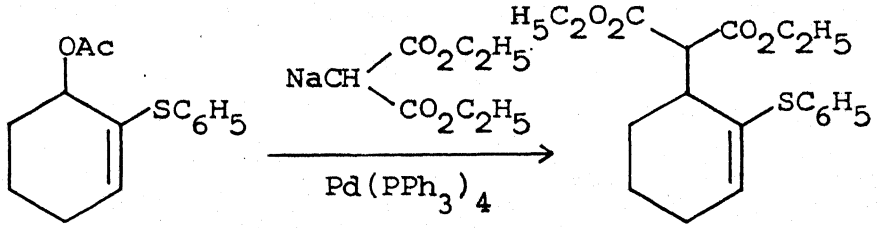
IR spectrum ν_{max}(neat): 1730 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.2 (t, J=7 Hz, 6H, CH_3), 2.0-2.43 (m, 2H, allylic CH_2), 3.0-3.4 (m, 1H, CH-CH=), 3.53 (d, J=5 Hz, 1H, $CH(CO_2C_2H_5)_2$), 4.03 (q, J=7 Hz, 4H, $COCH_2$), 5.6 (m, 1H, olefinic), 7.1 (m, 5H, aromatic).

Mass spectrum, m/e (rel.int.): 334 (37, M^+), 261 (10, $M^+-C_2H_5COOH$), 225 (100, $M^+-SC_6H_5$), 151 (50, $M^+-SC_6H_5$, $-C_2H_5COOH$), 187 (40, $M^+-2C_2H_5COOH$).

Anal. Calcd for $C_{18}H_{22}SO_4$: C, 64.67; H, 6.59; Found: C, 64.75; H, 6.52.

Preparation of 3-(αα-dicarboethoxy methyl)-2-phenylthiocyclohexene (31b)



30b 31b

Following the above described procedure the reaction of 30b (185 mg, 0.75 mmol) diethyl sodiomalonate [prepared from diethyl malonate (420 mg, 2.6 mmol) and sodium hydride (130 mg, 2.6 mmol)], triphenyl phosphine (60 mg, 0.23 mmol) and $Pd(PPh_3)_4$ (9 mg, 0.0075 mmol) in DMSO (5 mL) at room temperature for 30 h gave a crude product which was purified by column chromatography [eluent, pet.ether:ether (80:20)]. Yield 190 mg (73%).

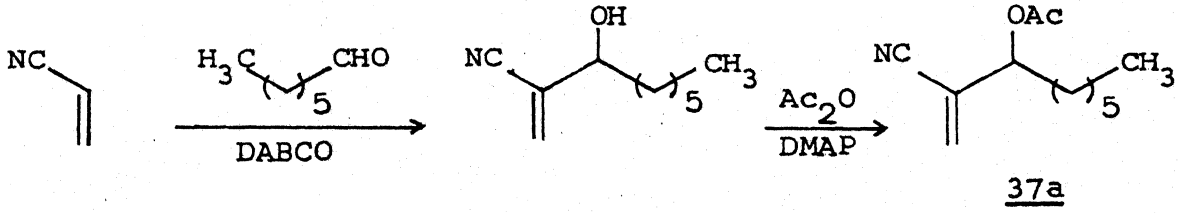
IR spectrum ν_{max}(neat): 1730 (C=O) cm^{-1}.

^{1}H NMR spectrum ($CDCl_3$): δ 1.23 (t, J=7 Hz, 6H, CH_3), 1.4-1.96 (m, 4H, CH_2), 1.96-2.4 (m, 2H, allylic CH_2), 2.73-3.2 (m, 1H, $\underline{CH}$-CH=), 3.9 (d, J=5 Hz, 1H, $\underline{CH}(CO_2C_2H_5)$, 4.13 (q, J=7 Hz, $\underline{CH_2}$, 4H), 6.23 (m, 1H, olefinic), 7.16 (m, 5H, aromatic).

Mass spectrum, m/e (rel.int.): 348 (100, M^+), 303 (60, $M^+-OC_2H_5$), 239 (38, $M^+-SC_6H_5$), 188 (100, $M^+-CH_2(CO_2C_2H_5)_2$).

Anal. Calcd for $C_{19}H_{24}SO_4$: C, 65.52; H, 6.90. Found: C, 65.70; H, 6.87.

Preparation of 2(1-acetoxyheptyl)acrylonitrile (37a)



37a

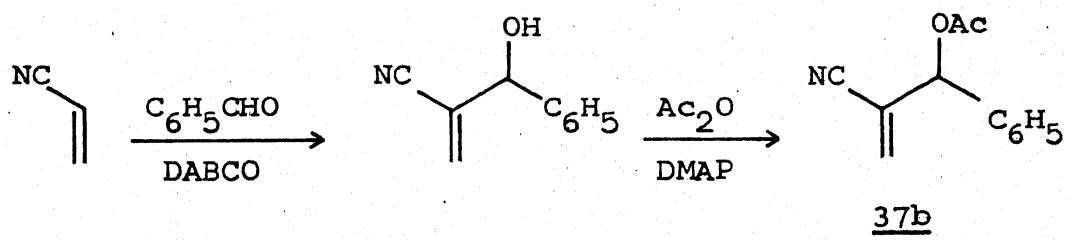
To a mixture of heptaldehyde (570 mg, 5 mmol) and acrylonitrile (0.5 mL, 7.5 mmol) was added 1,4 diazobicyclo(2.2.2)octane (DBACO) (84 mg, 0.75 mmol) and stirred at room temperature for 3 days. The reaction mixture was diluted with ether (25 mL), washed with 2N hydrochloric acid (5 mL), 10% sodium bicarbonate (5 mL), water (5 mL), brine (5 mL) and dried over anhydrous sodium sulphate. Removal of the solvent gave a crude alcohol which was acetylated using acetic anhydride (0.5 mL, 5.5 mmol) and

N,N(dimethyl)aminopyridine (DMAP) (cat. amount) in CH_2Cl_2 (3 mL) at room temperature for 3 h. The crude acetate was purified by column chromatography [eluent, pet.ether:ether (85:15)]. Yield, 850 mg (81%).

IR spectrum ν_{max}(neat): 2220 (C≡N), 1735 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 0.85 (t, J=6 Hz, 3H, CH_3), 1.18-1.56 (m, 8H, CH_2), 1.56-2 (m, 2H, CH_2), 2.05 (s, 3H, $COCH_3$), 5.2 (t, J=7 Hz, 1H, CHOAc), 5.93 and 6.0 (2s, 2H, olefinic).

Preparation of 2(1-acetoxybenzyl)acrylonitrile (37b)



37b

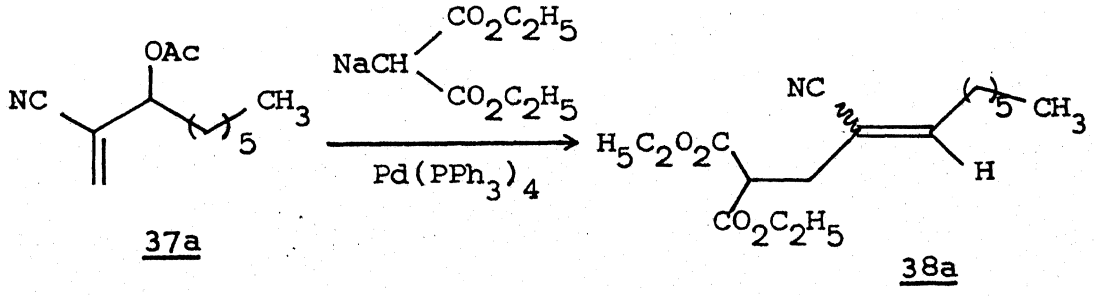
To a mixture of benzaldehyde (530 mg, 5 mmol) and acrylonitrile (0.5 mL, 7.5 mmol) was added DABCO (84 mg, 0.75 mmol) and stirred at room temperature for 40 h. The reaction mixture was diluted with ether (25 mL), washed with 2N hydrochloric acid (5 mL), aqueous sodium bicarbonate (5 mL), water (5 mL), brine (5 mL) and dried over anhydrous sodium sulphate. Removal of the solvent gave a crude alcohol which was acetylated using acetic anhydride (0.52 mL, 5.5 mmol) and N,N(dimethyl)aminopyridine (DMAP)

(cat. amount) in CH_2Cl_2 (2 mL) at room temperature for 2 h. The crude acetate was purified by column chromatography [eluent, pet. ether:ether (90:10)]. Yield, 650 mg (65%).

IR spectrum ν_{max}(neat): 2220 (C≡N), 1735 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 2.1 (s, 3H, $COCH_3$), 5.9 and 6.0 (2s, 2H, olefinic), 6.32 (s, 1H, CHOAc), 7.35 (m, 5H, aromatic).

Preparation of ethyl 2(carboethoxy)-4-cyanoundec-4-enoate (38a)



2(1-Acetoxyheptyl)acrylonitrile (37a) (209 mg, 1 mmol) in DMSO (0.5 mL) was added to a mixture of diethyl sodiomalonate [prepared from diethyl malonate (560 mg, 3.5 mmol) and NaH (175 mg, 3.5 mmol)], triphenylphosphine (78 mg, 0.3 mmol) and tetrakis(triphenylphosphine)palladium(0) (12 mg, 0.01 mmol) in DMSO (5 mL) at room temperature under nitrogen atmosphere. The resultant mixture was stirred at room temperature for 10 h, then it was diluted with water (5 mL), extracted with ether (3 x 15 mL), washed with water (5 mL) and dried over anhydrous sodium sulphate. Evaporation of

the solvent gave a crude product, which was purified by column chromatography [eluent, pet.ether:ether (80:20)]. Yield, 287 mg (93%).

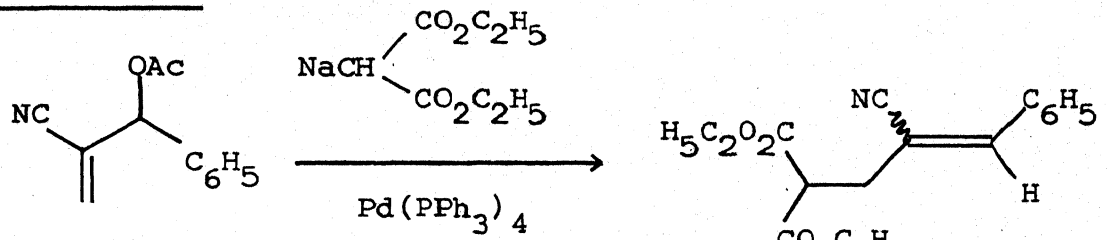
IR spectrum ν_{max}(neat): 2220 (C≡N), 1735 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 0.93 (t, 3H, J=7.5 Hz, CH_3), 1.06-1.63 (m,14H,CH_2 and CH_3), 2.0-2.56(m, 2H,allylic CH_2), 2.7(d, 2H, J=7.5 Hz, allylic, CH_2), 3.5 (t, 1H, J=7.5 Hz, $\underline{CH}(CO_2C_2H_5)_2$), 4.16 (q, J=7.5 Hz, 4H, $COC\underline{H}_2$), 6.0-6.36 (m, 1H, olefinic).

Mass spectrum, m/e: (rel.int.): 309 (40, M^+), 264 (45, $M^+-OC_2H_5$), 236 (30, $M^+-C_2H_5COOH$), 206 (50), 160 (100).

Anal. Calcd for $C_{17}H_{27}NO_4$: C, 66.02; H, 8.74; N, 4.53. Found: C, 66.20; H, 8.56; N, 4.62.

Preparation of ethyl-2(carboethoxy)-4-cyano-5-phenylpent-4-enoate (38b)



37b

38b

Following the above described procedure, the reaction of

37b (200 mg, 1 mmol) diethyl sodiomalonate [prepared from diethyl malonate (560 mg, 3.5 mmol) and NaH (175 mg, 3.5 mmol)], triphenylphosphine (78 mg, 0.3 mmol) and $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) in DMSO (5 mL) at room temperature for 12 h gave crude 38b which was purified by column chromatography [eluent, pet.ether:ether (85:15)]. Yield, 270 mg (90%).

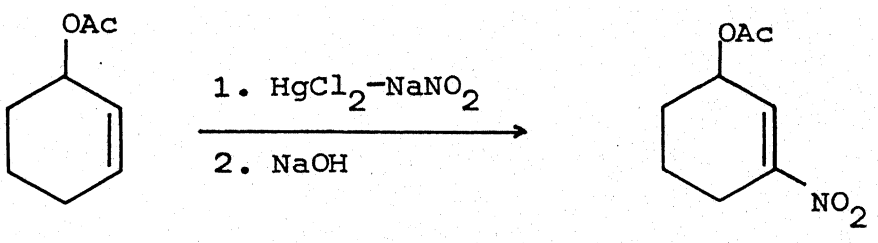
IR spectrum ν_{max}(neat): 2220 (C≡N), 1735 (C=O) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.26 (t, 6H, CH_3), 2.93 (t, 2H, allylic CH_2), 3.6 (t, 1H, C<u>H</u> $(CO_2C_2H_5)_2$), 4.2 (q, 4H, CH_2), 6.9 (s, 4H, CH_2), 6.9 (s, 1H, vinylic), 7.2-7.86 (m, 5H, aromatic).

Mass spectrum, m/e (rel.int.): 301 (85, M^+), 227 (26, $M^+-C_2H_5COOH$), 154 (100, $M^+-2C_2H_5COOH$).

Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.77; H, 6.31; N, 4.65. Found: C, 67.89; H, 6.45; N, 4.53.

Preparation of 1-acetoxy-3-nitrocyclohex-2-ene (41)



To a mixture of 1-acetoxycyclohex-2-ene (40) (280 mg, 2 mmol) in water (5 mL) were added sodium nitrite (300 mg, 4.1 mmol) and mercuric chloride (600 mg, 2.2 mmol) and it was stirred mechanically for 12 h. The resultant nitromercurial was filtered and washed with water and dissolved in CH_2Cl_2 (5 mL). Aqueous sodium hydroxide (2.5N, 0.8 mL) was added to the CH_2Cl_2 solution and stirred for 15 min. at room temperature. It was filtered through celite (to remove metallic mercury) and washed with CH_2Cl_2 (50 mL). The organic layer was washed with dil. hydrochloric acid (5 mL), water (10 mL), brine (10 mL) and dried over anhydrous sodium sulphate. Evaporation of the solvent gave a crude product which was purified by distillation. Yield, 195 mg (53%), b.p. 115-120°C/1 mm.

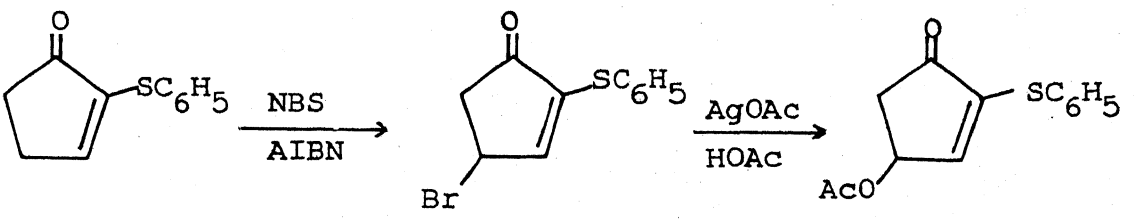
IR spectrum ν_{max}(neat): 1735 (C=O), 1515 (NO_2) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 1.8-2.0 (m, 4H, CH_2), 2.65 (m, 2H, allylic CH_2), 2.05 (s, 3H, $COCH_3$), 5.5 (m, 1H, C<u>H</u>-OAc), 7.1 (d, 1H, J=3 Hz, vinylic).

Mass spectrum, m/e (rel.int.): 143 (21, $M^+-CH_2=C=O$), 126 (8, M^+-CH_3COOH), 97 (25, M^+-CH_3COOH, $-CH_2=CH_2$).

Anal. Calcd for $C_8H_{11}NO_4$: C, 51.89; H, 5.95; N, 7.57. Found: C, 51.92; H, 5.73; N, 7.43.

Preparation of 4-acetoxy-2-phenylthiocyclopent-2-enone (46)



29a 46

A mixture of 2-phenylthiocyclopent-2-enone (29a) (2 g, 10.5 mmol), NBS (2.25 g, 12.6 mmol), AIBN (100 mg) in CCl_4 (15 mL) was refluxed for 2 h. After cooling in an ice-water bath, the mixture was filtered and the filter cake was washed with cold CCl_4. The filtrate was washed with water (2 x 10 mL), 10 % sodium thiosulphate (10 mL), brine (10 mL) and dried over anhydrous sodium sulphate. CCl_4 was removed under reduced pressure to obtain a crude bromo-enone. It was then (without further purification) treated with AgOAc (1.93 g, 11.5 mmol) in acetic acid (10 mL). The resultant mixture was stirred at room temperature for 12 h. Precipitated AgBr was filtered and acetic acid was removed under reduced pressure. The crude product was purified by column chromatography [eluent, pet.ether:ether (60:40)]. Yield, 1.4 g (54%).

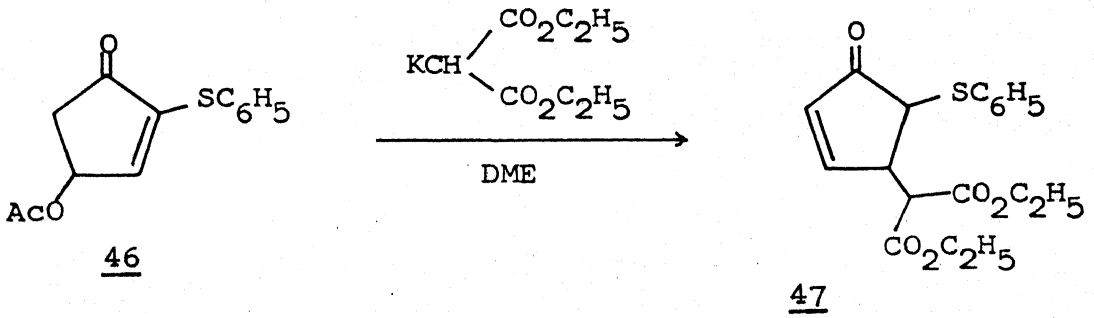
IR spectrum $\nu_{max}(CCl_4)$: 1740 ($\overset{O}{\overset{\|}{C}}-OCH_3$), 1720 ($\overset{O}{\overset{\|}{C}}-C=C$) cm^{-1}.

^1H NMR spectrum (CCl_4): δ 2.0 (s, 3H, $COCH_3$), 2.33 (dd, gem H, J=19 Hz, 2.5 Hz), 2.93 (dd, gem H, J=19 Hz, 6 Hz), 5.63 (m, 1H, CH-OAc), 6.46 (d, J=3 Hz, 1H, olefinic), 7.33 (m, 5H, aromatic).

Mass spectrum, m/e (rel.int.): 248 (75, M^+), 206 (28, $M^+-CH_2=C=O$), 189 (32, M^+-CH_3COOH), 161 (45), 128 (42).

Anal. Calcd for $C_{13}H_{12}SO_3$: C, 62.90; H, 4.84. Found: C, 62.82; H, 4.92.

Preparation of 3(αα-dicarboethoxy methyl)-2-phenylthiocyclopent-4-enone (47)



46 47

To a mixture of diethyl potassiomalonate [prepared from diethyl malanote (203 mg, 1.27 mmol) and potassium-t-butoxide (142 mg, 1.27 mmol)] in DME was added 46 (315 mg, 1.27 mmol). The resultant mixture was stirred at room temperature for 10 h. Addition of water (10 mL) followed by extraction with ether (3 x 15 mL) gave a crude product which was purified by column chromatography [eluent, benzene]. Yield, 240 mg (54%).

IR spectrum ν_{max}(neat): 1730 (br, C=O) cm^{-1}.

^{1}H NMR spectrum ($CDCl_3$): δ 1.28 (t, 6H, CH_3), 3.44-3.78 (m, 3H, C<u>H</u>-SC_6H_5, C<u>H</u>($CO_2C_2H_5$)$_2$ and allylic CH), 4.31 (q, 4H, CH_2), 6.31 (dd, J=6.2 Hz, 2.5 Hz, 1H, CH=C<u>H</u>-C=O), 7.16-7.84 (m, 6H, C<u>H</u>-CH-C=O and aromatic).

Mass spectrum, m/e (rel.int.): 348 (54, M^+), 274 (67, $M^+-C_2H_5COOH$), 188 (100, $M^+-CH_2(CO_2C_2H_5)_2$).

Anal. Calcd for $C_{18}H_{20}SO_5$: C, 62.07; H, 5.75. Found: C, 62.12; H, 5.80.

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